

FORMULATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF AMOXICILLIN TRIHYDRATE

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LIST OF ABBREVIATIONS

S.No.	Abbreviation	Full form
1	AMT	amoxicillin trihydrate
2	MSC	maximum safe concentration
3	MEC	minimum effective concentraton
4	APIs	active pharmaceutical ingredients
5	CDDS	controlled drug delivery systems
6	HAD	human drug absorption
7	AUC	area under the curve
8	GRDDS	gastro retentive drug delivery systems
9	CRDDS	controlled release drug delivery systems
10	GIT	gastro intestinal tract
11	MMC	migrating myoelectric cycle
12	GRT	gastro retention time
13	FDDS	floating drug delivery systems
14	HBS	hydrodynamically balanced system
15	PVA	poly vinyl alcohol
16	PMMA	polymethyl methacrylate
17	HPMC	hydroxyl propyl methyl cellulose
18	CMC	carboxy methyl cellulose
19	HPC	hydroxyl propyl cellulose
20	FT-IR	Fourier Transform Infrared (FT-IR) Spectroscopy
21	PVP	poly vinyl pyrrolidine
22	MCC	microcrystalline cellulose
23	CI	compressibility index

INTRODUCTION

1. INTRODUCTION

The oral route currently represents the most predominant and preferable route of drug delivery. Unlike majority of parenteral dosage forms, it allows ease of administration by the patient, and therefore a highly convenient way for substances to be introduced into the human body. Oral drug delivery systems have progressed from conventional immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action.

1.1 CONVENTIONAL DRUG DELIVERY SYSTEM

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms.

The oral dosage form has survived due to

1. Relatively simple and inexpensive to make
2. Convenient for the patient
3. Technology is easy to adapt to changing needs of the drug substance
4. Simplifies the regulatory approval process.

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption (Robinson JR Lee, 1987).

As can be seen from Figure 1, administration of the conventional dosage form by extra vascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

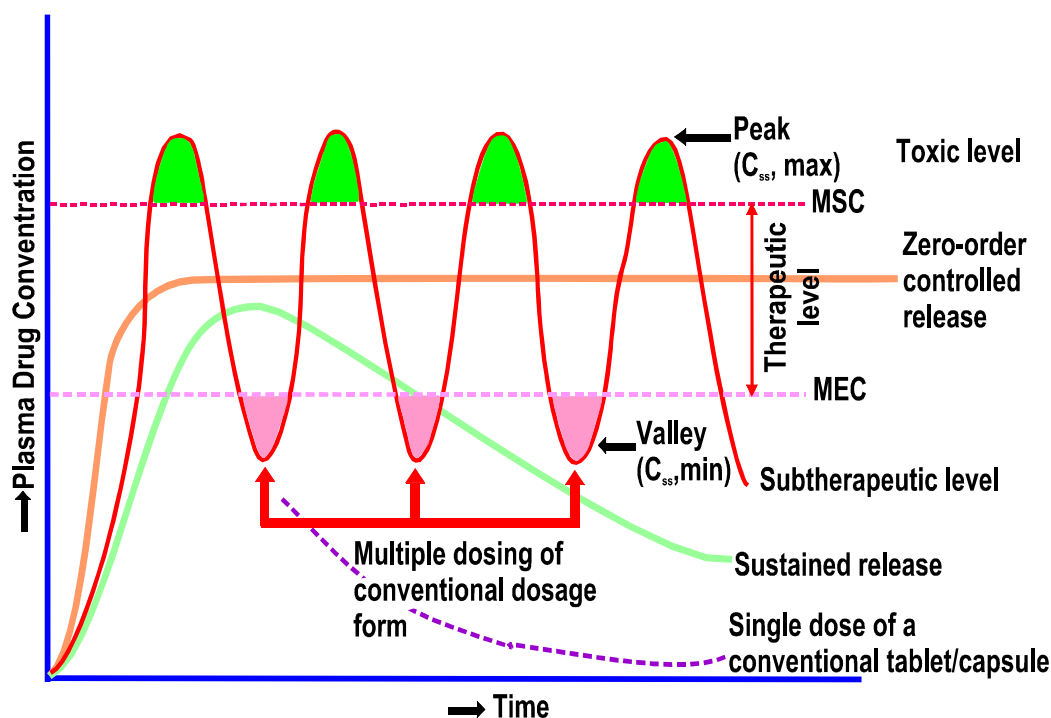


Figure 1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

Limitations of the Conventional Drug Delivery System:

- 1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
- 2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

- 3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.
- 4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits (Chien, 1992).

1.2 CONTROLLED DRUG DELIVERY SYSTEM (CDDS)

Over the years, as the expense and complications involved in marketing, new drug entities have increased with concomitant recognition of the therapeutic advantages of controlled drug delivery. Greater attention has been focused on the development of modified release dosage forms.

Modified release systems have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects. Oral modified release delivery systems are most commonly used for 1) delayed release (e.g., by using an enteric coating); 2) extended release (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile, triggered, etc.) and 4) site specific or timed release (e.g., for colonic delivery or gastric retention). Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release

kinetics. Delayed release dosage forms are distinguished from the ones mentioned above as they exhibit a pronounced lag time before the drug is released. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration. Extended release DDS include single-unit, such as tablets or capsules, and multiple-unit dosage forms, such as minitables, pellets, beads or granules, either as coated (reservoir) or matrix devices.

Controlled Release

Controlled release systems are designed to maintain plasma levels in therapeutic range and thus minimize the effects of such problems. Furthermore, controlled release systems reduce the dosing frequency, thereby improving patient compliance and therapeutic efficacy (Christopher et al., 2005).

Sustained Release

Drug products that provide “extended” or “sustained” drug release appeared as a major class of dosage form. Many terms as sustained-release, sustained-action, prolonged- action, controlled-release, extended-release, timed-release, and long-acting have been used to describe product types and features. For the most part, these terms are used to describe orally administered dosage forms, whereas the term rate-controlled delivery is applied to certain types of drug delivery systems in which the rate of drug delivery is controlled by features of the device rather than by physiological or environmental conditions as gastrointestinal pH or drug transit time through the gastro intestinal tract (GIT).

Modified-release, this term has come into general use to describe dosage forms having drug release features based on time, course, and/or location which are

designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate-release forms.

Extended-release, defines an extended-release dosage form as one that allows a reduction in dosing frequency to that presented by a conventional dosage form.

Delayed-release dosage form is designed to release the drug from the dosage form at a time other than promptly after administration. The delay may be time- based or based on the influence of environmental conditions, as gastrointestinal pH.

Controlled drug delivery systems (CDDS) offer several **advantages** compared to conventional DDS including:

- ✚ Avoiding drug level fluctuations by maintenance of optimal therapeutic plasma and tissue concentrations over prolonged time periods, avoiding sub-therapeutic as well as toxic concentrations, thus minimizing the risk of failure of the medical treatment and undesirable side effects;
- ✚ Reducing the administered dose while achieving comparable effects;
- ✚ Reduced frequency of administration leading to improved patients compliance and subsequently improved efficacy of the therapy and cost effectiveness;
- ✚ Targeting or timing of the drug action. Hence, it is highly desirable to develop CDDS releasing the drug at predetermined rates to achieve optimal drug levels at the site of action.

Disadvantages of CDDS

- Unpredictable or poor *in vitro*- *in vivo* correlation.
- Dose dumping.
- Reduced potential for dosage adjustment.
- Increased first pass clearance
- Poor systemic availability in general
- High cost.

An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity, and composition of the gastrointestinal fluids as it passes down the G.I tract. Considerable efforts have been made to design oral controlled drug delivery systems that produce more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, like inability to retain and localize the drug delivery system within desired regions of the G.I tract and highly variable nature of the gastric emptying process. The gastric emptying process can vary from a few minutes to 12 h, depending upon the physiological state of the subject and the design of pharmaceutical formulation. This variation may lead to unpredictable bioavailability and times to achieve peak plasma levels. In addition, the relatively brief gastric emptying time in humans, through the stomach or upper part of the intestine (Major absorption zone), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose.

1.3 ABSORPTION WINDOW

Some drugs display region-specific absorption that can be related to differential drug solubility and stability in different regions of the intestine as a result of changes in environmental pH, degradation by enzymes present in the lumen of the intestine or interaction with endogenous components such as bile. Active transport mechanisms for drugs involving carriers and pump systems have been well described.

Compounds such as ACE inhibitors and certain antibiotics exploit peptide transporters. The importance of P-450 metabolism in the intestinal mucosa has now been recognized. The isoform P4503A4 (CYP3A4) is dominant in 'gut wall' metabolism and different levels are found in different regions of the intestine. The absorption of drugs can also be limited by efflux mechanisms, especially if compounds are lipophilic in nature. The secretory transporter P-glycoprotein located on the mucosal surface of epithelial cells is responsible for the low and variable bioavailability of various compounds (e.g.-propranolol, felodipine). Some drugs can be substrate for both CYP3A4 and P-glycoprotein (cyclosporine, itraconazole). In theory, it should be possible to inhibit efflux and metabolism processes by the use of inhibitors, but such agents are not usually without their own pharmacological effects. The inhibitory effect of grapefruit juice toward intestinal CYP450 is a well known example.

Today, it is possible to assess regional differences in intestinal drug absorption by conducting non-invasive human drug absorption (HDA) study using a remote controlled delivery capsule. Gamma scintigraphy is used for real-time visualization of capsule location and a radiofrequency signal is used to activate the capsule at the target site. For example, in order to determine the bioavailability and pharmacokinetic profile of faropenem daloxate (a prodrug of broad spectrum antibiotic), this drug was delivered in a particulate form to the proximal small bowel, distal small bowel or ascending colon. The pharmacokinetic profiles for delivery to the two sites in the small intestine were similar and comparable to those for a reference tablet. Significant absorption was also seen after delivery to the colon, but the area under the curve (AUC) and the maximum plasma concentration (C_{\max}) values were markedly reduced.

Concept of absorption window

Drug exhibiting absorption from only a particular portion of GI tract or showing difference in absorption from various regions of GI tract are said to have regional variability in intestinal absorption. Such drugs show absorption window which signifies the regions of GI tract from where absorption primarily occurs. Drug released from the CRDDS after the

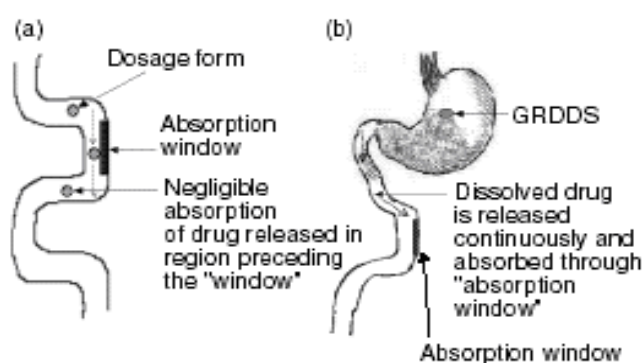


Figure 2: a) Conventional drug delivery system, (b) GRDDS.

absorption window has been crossed goes waste with no or negligible absorption occurring (Figure 2). This phenomenon drastically decreases the available drug for absorption, after release of drug from CRDDS. The CRDDS possessing the ability of being retained in the stomach are called GRDDS and they can help in optimizing the oral controlled delivery of drugs having absorption window by continuously releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability.

This absorption window is observed due to following factors

Physicochemical factors

pH- dependent solubility and stability

A drug experiences a pH range of 1-8 across the G.I tract and needs to be in solubilized form to successfully cross the biological membrane. Most of the drugs are passively absorbed in their un-ionized form and the extent of ionization at different pH values depends on solubility, stability and ionization by changing the physical properties of the drug in different portions of the G.I tract, can lead to regional variability in absorption of drugs.

Physiological factors***(a) Mechanism of absorption***

Perorally administered drugs are absorbed both by passive diffusion as well as by nonpassive means of absorption. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity due to the prevalence of these mechanisms only in a particular region of G.I tract.

(b) Metabolic Enzymes

Presence of certain enzymes in a particular region of G.I tract can also lead to regional variability in absorption of drugs that are substrates to those enzymes. Intestinal metabolic enzymes principally, phase I metabolizers like cytochrome P450 are abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with the levels rising slightly from the duodenum to the jejunum and then declining in the ileum and colon. This non-uniform distribution of cytochrome P450 causes regional variability in the absorption of drugs that are substrate to these enzymes.

1.4 GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Gastro-retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically, gastroretentive system retains in the stomach for a number of hours and continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Therefore, Sustained release DDS possessing gastric retention properties may be potentially useful.

1.4.1 ANATOMY AND PHYSIOLOGY OF THE GI TRACT

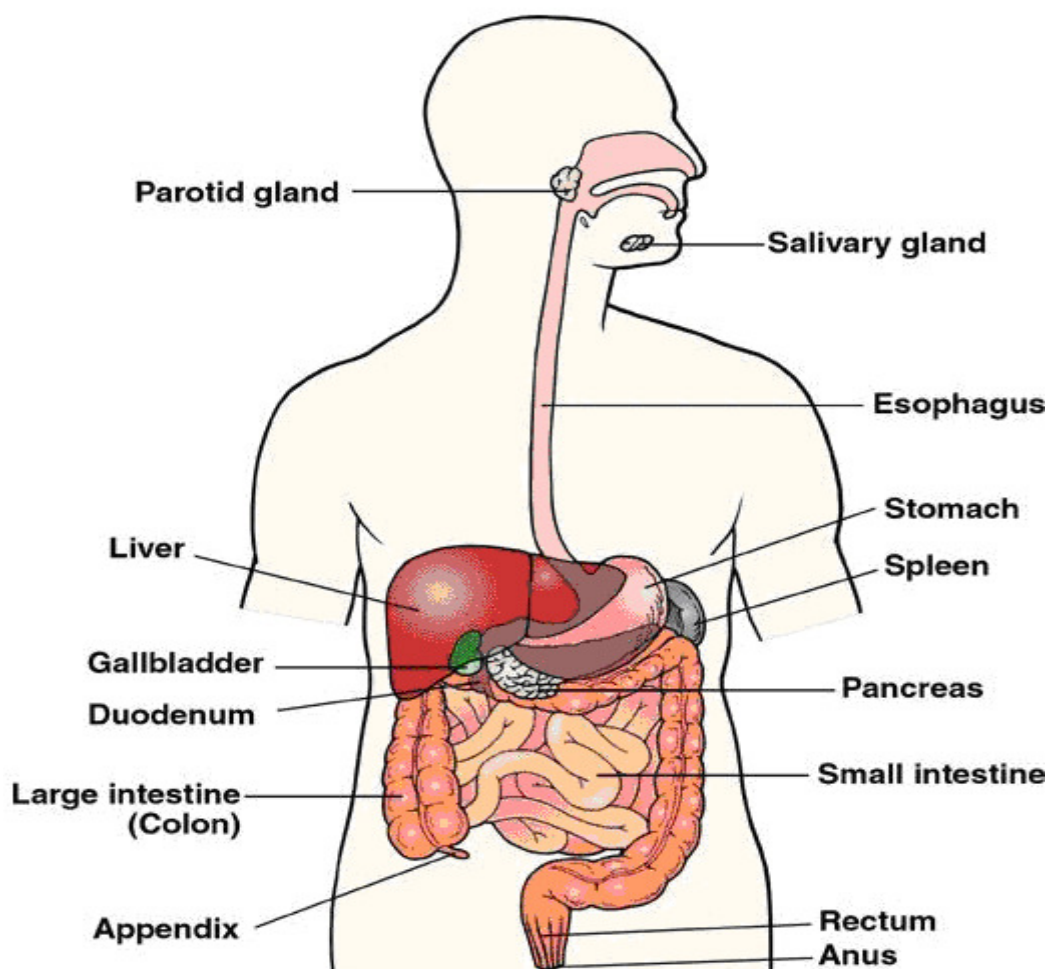


Figure 3: Structure of the gastrointestinal tract

To comprehend the considerations taken in the design of GRDFs and to evaluate their performance the relevant anatomy and physiology of the gastrointestinal tract must be fully understood. The basic Structure of the gastrointestinal tract is shown in Fig 3.

The GIT consists of a hollow muscular tube starting from the oral cavity, where food enters, the mouth, continuing through the pharynx, oesophagus, stomach and intestines to the rectum and anus. Anatomical and physiological features of the human GIT are given in Table 1.

Table 1: Anatomical and physiological features of the human GIT

Section	Avg length (cm)	Diameter (cm)	Villi present	Absorption mechanism	pH	Major constituents	Transit time of food (h)
Oral cavity	15-20	10	-	Passive diffusion, convective transport	5.2-6.8	Amylase, Maltase, Ptyalin, Mucins	Short
Esophagus	25	2.5	-	-	5-6	-	Very short
Stomach	20	15	-	Passive diffusion, convective transport	1.2-3.5	Hydrochloric acid, Pepsin, rennin, lipase, intrinsic factor	0.25-3
Duodenum	25	5	+	Passive diffusion, convective transport, active transport, facilitated transport, ion pair, pinocytosis	4.6-6	Bile, Trypsin, chymo trypsin, amylase, maltase, lipase, nuclease, CYP 3A4	1-2
Jejunum	300	5	++	Passive diffusion, convective transport, active transport, facilitated transport	6.3-7.3	Amylase, maltase, lactase, sucrose, CYP 3A5	-

Ileum	300	2.5-5	++	Passive diffusion, convective transport, active transport, facilitated transport	7.6	Lipase, nuclease, nucleotidase,ent ro kinase	1-10
Cecum	10-30	7	+	Passive diffusion, convective transport, active transport, Pinocytosis	7.5-8	-	Short
Colon	150	5	-	Passive diffusion, convective transport, active transport	7.6-8	-	4-20
Rectum	15-19	2.5	-	Passive diffusion, convective transport, active transport, Pinocytosis	7.5-8	-	Variable

Stomach

The stomach is situated in the left upper part of the abdominal cavity under the diaphragm, between the lower end of the esophagus and the small intestine, and is the most dilated part of the GIT. Its opening to the duodenum is controlled by the pyloric sphincter. The stomach is divided into three anatomical regions (Figure 4).

- i) Fundus
- ii) Body and
- iii) Pylorus (or antrum)

The proximal stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. (Tortora et al., 1996; Wilson and Waugh, 1989).

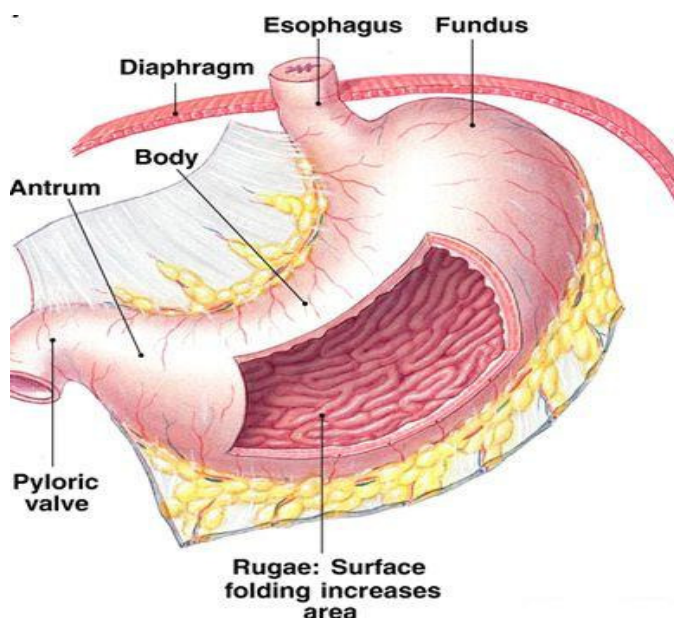


Figure 4: Schematic illustration of the stomach anatomical structure.

Small Intestine

The small intestine is composed of the duodenum, jejunum, and ileum. It averages approximately 6m in length. The duodenum is the proximal C-shaped section that curves around the head of the pancreas. The duodenum serves a mixing function as it combines digestive secretions from the pancreas and liver with the contents expelled from the stomach. The start of the jejunum is marked by a sharp bend, the duodenojejunal flexure. It is in the jejunum where the majority of digestion and absorption occurs. The final portion, the ileum, is the longest segment and

empties into the caecum at the ileocaecal junction. The small intestine has a large surface area, which is comparable to the area of a basketball court, 463 m². This is the main reason it is the primary absorption site of water, ions, vitamins and nutrients such as amino acids, fats and sugars. In addition, the digestion of fats, peptides and sugars occurs in this segment of the gastrointestinal tract. The pH of the small intestine is 6–7. The transit time in the small intestine is long, relatively constant and is unaffected by food.

Large Intestine

The colon has some absorption properties of water and ions. Certain drugs and especially peptide molecules are also absorbed. This is despite the lack of villi, which leads to small surface area.

Gastric emptying

The time a dosage form takes to traverse the stomach is usually termed the ‘gastric emptying rate’. Gastric emptying of Pharmaceuticals is highly variable and is dependent on dosage form. The process of gastric emptying occurs during fasting as well as fed states. However, the pattern of motility is distinct in the 2 states. In the fasting state, it is characterized by an interdigestive series of electrical events that cycle both through stomach and small intestine every 2 to 3 hours. This activity is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 consecutive phases (Figure 5) as described by Wilson and Washington.

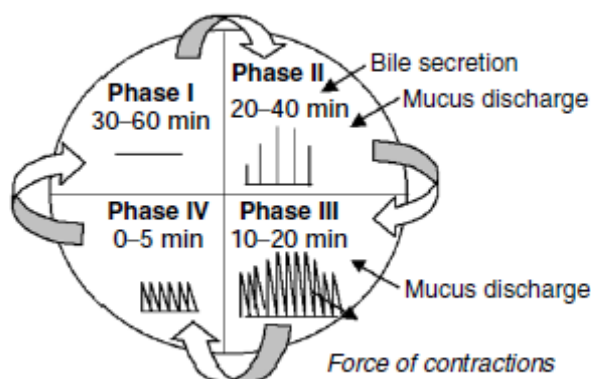


Figure 5: Motility patterns of the GIT in the fasted state.

- **Phase I (Basal phase)** lasts from 30 to 60 minutes with rare contractions.
- **Phase II (Preburst phase)** lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- **Phase III (Burst phase)** lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
 - **Phase IV** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

The motor activity in the fed state is induced 5-10 min after ingestion of a meal and persists as long as food remains in the stomach. It consists of regular and frequent contractions. These contractions are not as severe as those in the third phase of the fasted motility pattern. The G.I. Transit times of dosage forms in the various segments of the G.I. tract are listed in **Table 2**.

Table 2: Transit times of various dosage forms across the segments of the GIT.

Dosage forms	Transit time(h)		
	Stomach	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8

Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Solution	0.3±0.07	4.1±0.5	4.4

Gastric pH

The gastric pH is influenced by many factors like diet, disease, presence of gases or fatty acids, and other fermentation products (Rubinstein, 1990), age (Varis et al., 1979), pathological conditions drugs, as well as intra- and inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs. Radiotelemetry, a noninvasive device, has successfully been used to measure the gastrointestinal pH in humans. It has been reported that the mean value of gastric pH in fasted healthy males is 1.7 ± 0.3 (Chung et al., 1986; Dressman et al., 1990; Russell et al., 1993), while that of females was reported to be slightly lower (Charman et al., 1997; Feldman and Barnett, 1991). On the other hand, in the fed state, the mean gastric pH in healthy males has been reported to be between 4.3 – 5.4 (Dressman et al., 1990), and the pH returned to basal level in about 2 to 4 hours.

About 20% of the elderly people exhibit either diminished (hypochlorohydia) or no gastric acid secretion (achlorohydia) leading to basal pH value over 5.0 (Varis et al., 1979). Pathological conditions such as pernicious anemia and AIDS may significantly reduce gastric acid secretion leading to elevated gastric pH (Holt et al., 1989; Lake-Bakaar et al., 1988). In addition, drugs like H₂ receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion.

Hence, the gastric pH is an important consideration when selecting a drug substance, excipients, and drug carrier for designing intragastric delivery systems.

1.4.2 FACTORS AFFECTING GASTRIC RETENTION OF DOSAGE FORMS

- ❖ **Density:** Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density of a dosage form which affects the gastric emptying rate. A buoyant dosage form should have a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

- ❖ **Size:** Dosage form units having a diameter of more than 7.5 mm are reported to have an increased gastric residence time compared with those having a diameter of 9.9 mm. Gastric retention time of a dosage form in the fed state can also be influenced by its size. Small tablets are emptied from the stomach during the digestive phase while large size units are expelled during the house keeping waves.

- ❖ **Shape of dosage form:** Different shapes (ring, tetrahedron, cloverleaf, disk, string and pellet) displays different gastric retention times, due to their size and geometry of the systems. The tetrahedron resided in the stomach for longer periods than other devices of a similar size; likewise extended gastric retention was observed with rigid rings .Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) have a better gastric residence time as compared with other shapes and had been reported to have better (GRT 90% to 100% retention at 24 hours compared with other shapes).

- ❖ **Single or multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles

or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- ❖ **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

- ❖ **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release. (Timmermans et al, 1994)

- ❖ **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats. (Marvola et al., 1989).

- ❖ **Frequency of feed:** The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

- ❖ **Gender:** Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.
- ❖ **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
- ❖ **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- ❖ **Concomitant drug administration:** Anticholinergics like atropine and Propantheline, opiates like codeine and prokinetic agents like Metoclopramide and Cisapride (Mojave Ian et al., 1988) can affect the gastric retention time.
- ❖ **Biological factors:** Diabetes and Crohn's disease can affect the gastric retention time.

1.4.3 DRUG CANDIDATES FOR GASTRIC RETENTION

Gastroretentive DDSs exhibiting controlled drug release are significantly important for drugs which are:

- Acting locally in the stomach (e.g. antibiotics against *Helicobacter Pylori*, antacids and Misoprostol) (Burton et al., 1995; Fabregas et al., 1994; Oth et al., 1992; Whitehead et al., 2000; Whitehead et al., 1996).

- Absorbed incompletely due to a relatively narrow window of absorption in the GIT, such as Cyclosporin, Ciprofloxacin, Furosemide, L-DOPA, *P*-aminobenzoic acid and Riboflavin (Drewe et al., 1992; Erni and Held, 1987; Harder et al., 1990; Hoffman et al., 2004; Ichikawa et al., 1991a; Klausner et al., 2003d; Levy and Jusko, 1966; Rouge et al., 1996).
- Unstable in the intestinal or colonic environment such as Captopril (Matharu and Sanghavi, 1992) or
- Exhibit low solubility at high pH values such as Verapamil HCl, Diazepam and Chlordiazepoxide (Chen and Hao, 1998; Elkheshen et al., 2004; Sheth and Tossounian, 1984; Soppimath et al., 2001).

In general the group of drugs, that benefits from an oral application using a gastroretentive DDS, includes analgesics, antibiotics, tranquilizers, diuretics, antidepressants, vitamins, hormones, antacids and antiparkinsonian drugs (Hoichman et al., 2004).

Gastroretentive DDS, on the other hand, are not suitable for drugs that may cause gastric lesions, e.g., non-steroidal anti-inflammatory agents and drug substances that are unstable in the strong acidic environment of the stomach. In addition, gastroretentive systems do not offer significant advantages over conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract (Talukder and Fassihi, 2004). It is recognized, however, that there are many physiological constraints which may limit development of such delivery systems.

1.4.4 APPROACHES TO GASTRIC RETENTION

Various approaches have been pursued to increase the retention of oral dosage forms in the stomach. The most common approaches used to increase the gastric residence time of pharmaceutical dosage forms include

- Floating systems
- Swelling and expanding systems
- Bioadhesive systems
- Unfolding and modified- shape systems
- High density systems
- Others

1.4.4.1 Floating Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (mechanism given in Figure 6), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased

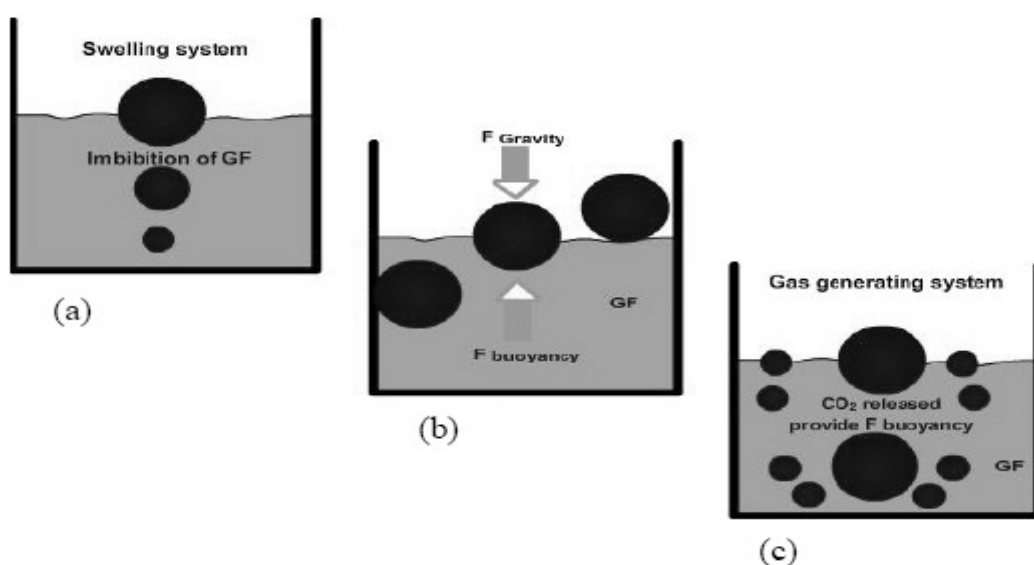


Figure 6: Mechanism of floating systems

GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.

Most floating systems reported in the literature are single unit systems, such as HBS and floating tablets. The systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered due to their all or nothing emptying process (Kawashima et al., 1991). On the other hand, multiple unit dosage forms, such as hollow microsphere (microballoons), granules, powder, and pellets, are more suitable since they are claimed to reduce the inter- and intra-subject variability in absorption and reduce the probability of dose dumping (Rouge et al., 1997).

Types of floating drug delivery systems (FDDS)

Floating properties based on the mechanism of buoyancy are divided into:

1. **Non effervescent systems** with inherent low density due to swelling; and
2. **Effervescent systems** with low density due to gas generation and entrapment.

1.4.4.1.1 Non- Effervescent Systems

A) Hydrodynamically Balanced Systems

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface (Dubernet et al., 2004). Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Reddy et al., 2002)(Figure7).

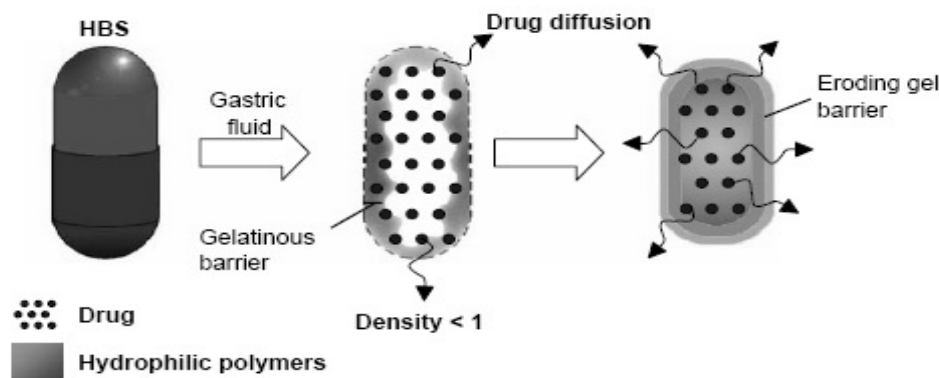


Figure 7: Hydrodynamically balanced system

Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazepoxide hydrochloride. The drug is a classical example of a solubility problem wherein it exhibits a 4000-fold difference in solubility going from pH 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/mL at acidic pH and is ~0.1 mg/mL at neutral pH).

B) Alginate Beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium

chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

C) Hollow Microspheres / Microballons:

Hollow microspheres loaded with drug in their outer polymer shell were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40°C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h *in vitro* (Kawashima, 1992).

Floating microparticles based on low-density foam powder has been proposed and its performance investigated *in vitro* (Streubel et al., 2002). The floating microparticles were prepared with an oil-in-water solvent extraction/evaporation method and were composed of polypropylene foam powder; verapamil HCl as the model drug; and a controlled release polymer, Eudragit® RS, EC or polymethyl methacrylate (PMMA). The microparticles were irregular in shape and highly porous. Good *in vitro* floating behavior was observed. The increase in drug release was proportional to the drug loading and inversely proportional to the amount of polymer and the release profile varied with varying the polymer type.

1.4.4.1.2 Effervescent Systems (Gas-Generating Systems):

This approach provides floating drug delivery systems based on the formation of CO₂ gas. It utilizes effervescent components such as sodium bicarbonate (NaHCO₃) or sodium carbonate, and additionally citric or tartaric acid (Rubinstein and Friend, 1994). Alternatively matrices containing chambers of liquids that gasify at body temperature could be used. Upon contact with the acidic environment, a gas is liberated, which produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on gastric contents.

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc. (Rubinstein A et al., 1994; Stockwell AF et al., 1986).

Ichikawa *et al* developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in

the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO₂ was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml. It was found that the system had good floating ability, independent of pH and viscosity and the drug released in a sustained manner (Figure 8).

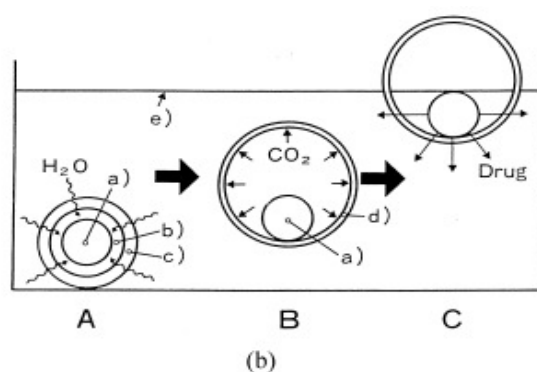
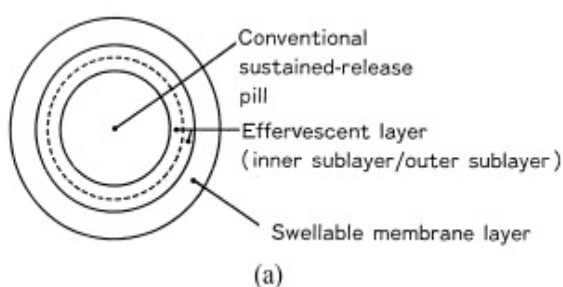


Figure 8: (a) A multi-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO₂ and floating; (C) Dissolution of drug.

Table 3: List of drugs prepared as FDSS

S.No.	DOSAGE FORM	DRUGS
1.	Microspheres	Metformin hydrochloride, ketoprofen, Aspirin, Verapamil, Griseofulvin, <i>P</i> -nitroaniline, Ibuprofen,
2.	Granules	Diclofenac sodium, Indomethacin, Prednisolone
3.	Capsules	Chlordiazepoxide HCl, Diazepam, Frusemide, L-Dopa and Benserazide, Misoprostol, Propranolol
4.	Tablets/Pills	Phenytoin hydrochloride, 5-fluorouracil, Furosemide,.

TABLE 4: LIST OF DRUGS WHICH ARE MARKETING AS FDDS

Brand name	Drug	Clinical Importance	Dosage form
Madopar [®]	Levodopa Benserazide	Parkinsonism	Capsule
Cytotec [®]	Misoprostal	Gastric ulcer	Capsule
Valrelease [®]	Diazepam	Sedative –hypnotic	Capsule
Convion	Ferrous sulphate	Pernicious anemia	Capsule
Liquid Gavison [®]	Al. hydroxide, Mg. carbonate	Heart burn	Liquid alginate preparation
Topalkan [®]	Al-Mg antacid	Antacid	Liquid alginate preparation
Cifran OD [®]	Ciprofloxacin	Urinary tract infection	Tablet
Oflin OD [®]	Ofloxacin	Genital Urinary, respiratory, Gastro-intestinal infection	Tablet
Prolopa [®]	Propranolol	Hypertension	Tablet
Amalgate Flotacoat [®]	Amalgate	Antacid	Tablet

Halo™	Propranolol	Hypertension	Tablet
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Raft-Forming Systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO₂ bubbles (Figure 9) on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment.

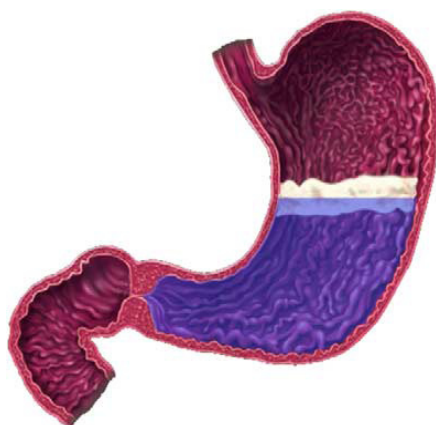


Figure 9: Schematic illustration of the barrier formed by a raft-forming system

Low-density systems

1.4.4.2 Swelling and Expanding Systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter (Caldwell et al., 1988). However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral

intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release.

The expansion of this type of DDS is generally due to the presence of specific hydrogel formers, which after swallowing; drastically increase in size upon contact with aqueous media. This increase in size prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as the “*plug type systems*” since they exhibit a tendency to remain lodged at the pyloric sphincter. Caldwell et al., 1988 proposed different geometric forms (tetrahedron, ring or planar membrane (4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule.

1.4.4.3 Bioadhesive Systems

This approach is used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. A bioadhesive can be defined as a substance with the ability to interact with biological materials and is capable of being retained on the biological substrate for a period of time. Bioadhesion always occurs in the presence of water (Andrews et al., 2009).

It involves the use of bioadhesive polymers that can adhere to the epithelial surface of the GIT. These are usually macromolecular, hydrophilic gelling substances with numerous hydrogen-bond forming groups, such as carboxyl, hydroxyl, amide and sulfate groups (e.g., crosslinked polyacrylic acids, sodium carboxymethyl cellulose (CMC), sodium alginate and carrageenan). A broad spectrum of polymers was studied for their bioadhesive properties. It was concluded that anionic polymers have better binding capacity than neutral or cationic polymers (Lehr, 1994; Gupta et al., 1990). The proposed mechanism of bioadhesion is the formation of hydrogen –

and electrostatic bonding at the mucus-polymer boundary (Gupta et al., 1990), although it is not yet clear. Rapid hydration in contact with the muco-epithelial surface appears to favour adhesion.

1.4.4.4 Unfolding and Modified- Shape Systems

These are non disintegrating geometric shapes moulded from silastic elastomer or extruded from polyethylene blends, which extend the gastric residence time depending on size, shape and flexural modulus of the drug delivery device (Caldwell, 1988a, 1988c; Cargill et al., 1988; Fix et al., 1993; Kedzierewicz et al., 1999).

These systems consist of at least one erodible polymer (e.g., Eudragit® E, hydroxypropyl cellulose (HPC)), one nonerodible polymer (e.g., polyamides, polyolefins, polyurethanes), and a drug dispersed within the polymer matrix. Cloverleaf, disk, string and pellet shapes were moulded from silastic elastomer, while tetrahedron and rigid-ring shapes were fabricated from blends of low-density polyethylene and ethylene: vinyl acetate copolymer. The devices are compressible to a size suitable for swallowing within a capsule, and are self-expandable to a size, which prevents their passage through the pylorus. Furthermore, they are sufficiently resistant to forces of the stomach to prevent rapid passage through the pylorus for a pre-determined period of time, and erode in the presence of gastric juices.

In vivo studies in beagle dogs have been performed to study the systems physical characteristics, such as size, shape and flexibility on the gastric emptying (Cargill et al., 1988), after they were folded and placed in a gelatin capsule. The tetrahedron-shaped devices remained in the stomach for longer periods of time than the other shapes, while strings and pellets were eliminated fairly rapidly.

Other shapes, which can be packed into gelatin capsules and increase in size following unfolding, include Y-shaped systems (Sonobe, 1995) and sheet-like shaped devices (Brewer, 1980).

1.4.4.5 High Density Systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm³) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm³ (Bechgaard H, et al., 1978).

1.4.4.6 Magnetic Systems

This system is based on a simple idea: The dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito et al., 1990 used this technique in the rabbits with bioadhesive granules containing ultra fine Ferrite (γ -Fe₂O₃). This guided them to the esophagus with an external magnet (~1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 hrs. Fujmori et al., 1994 formulated a magnetic tablet containing 50% w/w ultra ferrite with hydroxypropylcellulose and Cinnarazine.

1.4.5 ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage forms at the site of absorption and thus enhances the Bioavailability. These are summarized as follows.

I. Sustained Drug Delivery

Sustained drug absorption from oral controlled release dosage form is often limited due to short gastric retention time. However, GFDDS remain in the stomach for several hours to their increased GRT. It has been suggested that due to their low density than their gastric contents and relatively large size they do not pass through the pylorus that has an opening of approximately 0.9-1.9cm. It has been observed that major portion of drug releases in the colon rather than the stomach in case of modified release capsule. However, prolongation in the GRT may sustain the drug .release behaviour.

II. Site Specific Drug Delivery

Drugs having absorption sites in the upper small intestine like furosemide and riboflavin are typically formulated in the floating dosage forms. It has been reported that absorption of furosemide takes place mainly through stomach followed by duodenum. This characteristics of furosemide prompted scientists to develop a monolithic floating system, which could prolong the GRT and thereby increase the Bioavailability. GFDDS serves as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these

dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted.

A bilayer-floating capsule has been developed for local delivery of misoprostol to the gastric mucosa for prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs). Mechanistically, the drug replenishes the GI-protective prostaglandins that are depleted by NSAIDs. Therefore, sustained and controlled delivery of misoprostol to the stomach provides sufficient local therapeutic levels. This in turn reduces the side effects caused by the presence of the drug in systematic circulation (uterotonic activity) and also retards diarrhoea, which is the result of combination of intestinal and systematic exposure of drug. Moreover, the prolonged gastric availability of the misoprostol from FDDS also reduces the dosing frequency. 5-Fluorouracil bearing floating tablets have been successfully evaluated in four patients with stomach neoplasms.

III. Absorption or Bioavailability Enhancement

Drugs that have poor Bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the Bioavailability of floating dosage forms could be achieved.

IV. Fewer Doses: Creating once daily formulations for improved patient compliance.

V. Improved plasma levels: Both extends plasma concentration levels and provides a more linear release profile.

VI. Better Bioavailability: Delivers the drug in the upper G.I. tract for optimal absorption.

VII. Less Irritation: The polymer matrix acts as a buffer between harsh drug crystals and the stomach lining.

VIII. Fewer side effects: Keeps drugs out of the lower GI tract which can be harmful to intestinal flora. Lower peak concentrations can also reduce adverse pharmacological effects.

IX. Low risk inactive ingredients: Tablets are composed of well understood polymers from the FDA's inactive ingredients list. This keeps the regulatory risks and hurdles of the formulation to an absolute minimum.

X. Manufacturing ease: Tablets are made in standard high-speed tableting equipment. No special tooling or engineering is required. This enables high quality, consistent, rapid scale-up and technology transfer to our development and marketing partners.

XI. Low cost: The ingredients used in these systems are commodity items, produced in extremely large quantity and at very low cost.

1.4.6 DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

1. There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted.
2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
3. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system (Hou et al., 2003).
4. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted exactly or accurately.
5. Gastric emptying of floating forms in supine subjects may occur at random and become highly dependent on the diameter. Therefore, patients should not be dosed with floating forms just before going to bed.
6. High variability in gastric emptying time due to variations in emptying process.
7. Unpredictable bioavailability.

1.4.7 LIMITATIONS

1. The major disadvantage of floating systems is requirement of a sufficiently high level of fluids in the stomach for the drug delivery i.e. upto 400ml of gastric fluids should be present for optimum buoyancy. However, this limitation can be overcome by coating the dosage form with bioadhesive

polymers, which easily adhere to the mucosal lining of the stomach and retain.

The dosage form can be administered with a glass full of water (200-250 ml) to provide the initial fluid for buoyancy.

2. Floating system is not feasible for those drugs that have solubility problems in gastric fluids.
3. Drugs that are not stable at gastric pH are not suitable candidates to be formulated as GRDDS.
4. Drugs that irritate the mucosa are not suitable candidates and should be avoided to be formulated as GRDDS.
5. The drugs, which have multiple absorption sites in the gastrointestinal tract and are absorbed throughout gastrointestinal tract, which under significant first pass metabolism, are not desirable candidates.
6. Some drugs present in the floating system cause irritation to gastric mucosa.
7. Single unit floating capsules or tablets are associated with an all or none concept, but this can be overcome by formulating multiple unit systems like floating microspheres or microballoons.

1.4.8 EVALUATION OF GRDDS

Any drug product must be evaluated to ensure its performance characteristics and to control batch-to-batch quality. In addition to routine tests for general

appearance, hardness, friability, drug content, weight variation, uniformity of content, disintegration time, and drug release, the gastroretentive performance of GRDDS must be evaluated.

1.4.8.1 Floating Systems

Floating/buoyancy time: The test for buoyancy is usually determined in 900 mL of simulated gastric (HCl/NaCl with 0.02% Tween 80, pH 1.2) or intestinal fluids KH₂PO₄/NaOH buffer with 0.02% Tween 80, pH 7.4) maintained at 37°C using the USP dissolution apparatus. These fluids simulate the surface tension of human gastric juice (35–50 mN/m²). The amount of time the dosage form floats is termed the *floating time*. In the case of floating microparticles, the number of floating particles and the time during which they remain buoyant on the test solution can be determined. The floating process depends on the balance between the weight and volume of the dosage form. An increase in the buoyancy force caused by the increased volume causes a resultant weight increase and leads to dosage-form flotation.

Specific gravity: The specific gravity of floating systems can be determined by the displacement method, using benzene as a displacing medium.

1.4.8.2 Bio/Mucoadhesion Systems

Bioadhesive strength: The bioadhesive strength of a polymer can be determined by measuring the force required to separate the polymer specimen sandwiched between the layers of either an artificial (e.g., cellophane) or biological (e.g., rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an automated texture analyzer.

1.4.8.3 Swelling Systems

Weight gain and water uptake (WU): The swelling behaviour of a dosage unit can be measured by studying its weight gain or WU. The study is done by immersing the dosage form in simulated gastric fluid at 37°C and determining these factors at regular intervals. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. WU is measured in terms of percent weight gain, as given by the following equation

$$\text{WU} = (W_t - W_0) \times 100/W_0$$

In which, W_t and W_0 are the weights of the dosage form at time t and initially, respectively. Furthermore, the GRDDS should be evaluated for gastroretention and drug-release behaviour.

1.4.9 METHODS TO ASSESS *IN-VIVO* GASTRO-RETENTION OF GRDDS

Unlike other formulations, the kinetics of transit of the GRDF along the GI tract, and especially in determining its GRT are very important. It requires, in most cases, an imaging technique that can locate the GRDF in vivo. The following methods have been utilized so far to assess gastro-retentivity.

i) Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a noninvasive technique that is not associated with radioactivity and allows observation of the total anatomical structure in relatively high resolution. The visualization of the GI tract by MRI has to be further improved by the administration of contrast media. For solid DFs, the incorporation of

a super paramagnetic compound such as ferrous oxide enables their visualization by MRI. The technique is safe and allows obtaining many pictures from the same subject.

ii) Radiology (X-ray)

In this technique, a radio-opaque material has to be incorporated in the DF, and its location is tracked by X-ray pictures. The technique is used to evaluate gastroretentivity of GRDFs and the disintegration rate of DFs *in vivo*, and also to determine the esophageal transit. Although it is considered cheap and a simple method to use, its major disadvantage is the safety issue owing to repeated exposure to X-ray that increase the risk for the volunteers.

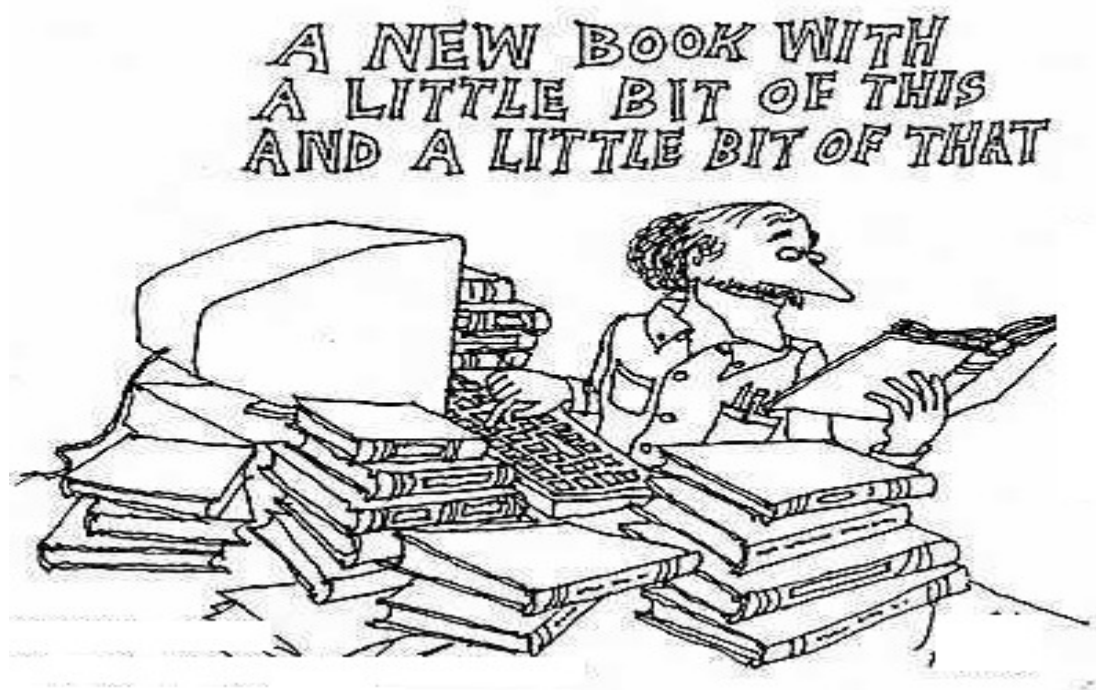
iii) γ - Scintigraphy

Gamma scintigraphy relies on the administration of a DF containing a small amount of radioisotope, e.g., ^{152}Sm , which is a gamma ray emitter with a relatively short half-life. The isotope has to be incorporated into the GRDF in advance. Then, a short time prior to the study, the formulation has to be irradiated in a neutron source that causes it to emit γ rays. The emitted ray can be imaged using a “gamma camera”-a form of a scintillation counter, combined with a computer to process the image, and thereby the DF can be tracked in the GI tract. This technique is elegant and provides proper assessment of gastroretentivity in humans.

iv) Gastroscopy

Gastroscopy is commonly used for the diagnosis and monitoring of the GI tract. This technique utilizes a fiber optic or video system and can be easily applied for

monitoring and locating GRDFs in the stomach. However, it is too inconvenient to conduct the procedure frequently in the same experiment for one subject. In human, the procedure can be applied with or without slight anesthesia while it requires complete anesthesia in dogs.



LITERATURE REVIEW

2. LITERATURE REVIEW

Dennis et al. (1992) described a buoyant controlled release powder formulation, which may be either filled into capsules or compressed into tablets. The formulation consisted of a drug of basic character, a pH dependent polymer, sodium or potassium alginate, a pH independent hydrocolloid gelling agent such as HPMC, methylcellulose, HPC or a mixture of two or more, and a binder. The formulation was considered unique in the sense that it released the drug at a controlled rate regardless of the pH of the environment, being free of calcium ion and carbon dioxide (CO₂) producing material, and had drug release properties similar to a tablet of identical composition.

Yuasa et al. (1996) developed intragastric floating and sustained release granules of Diclofenac sodium using a polymer solution of HPC-L grade and EC, and calcium silicate as a floating carrier, which has a characteristically porous structure. The coated granules acquired floating ability from the air trapped in the pores of calcium silicate when they were coated with a polymer.

Whitehead et al. (1996) developed multiple unit floating freeze dried calcium alginate beads. These beads maintained a positive floating force for over 12 hrs, and the density measurement, using a helium pycnometer, was less than 1 g/cm. The *in vivo* behavior of this system compared to non-floating multiple-unit dosage forms manufactured from identical material have also been performed using γ -scintigraphy in the fed state (Whitehead et al., 1998). Prolonged gastric residence times of over 5.5 h were achieved for the floating formulations, while the non-floating beads displayed short gastric residence times, with a mean onset emptying time of 1 hr.

A glycerol monooleate (GMO) matrix was recently proposed as a gastroretentive carrier system by *Kumar et al. (2004)*. The GMO matrices were prepared by melting GMO at 55°C in a water bath, adding the drug under stirring and pouring the molten mass into cylindrical moulds. The GMO matrices significantly swelled in water and the swollen mass floated at the surface after a certain lag time.

Floating tablets using the anionic exchange resin, cholestyramine, was described by *Todd et al. (1979)*. The directly compressed tablet was composed of granules containing anhydrous cholestyramine, low viscosity grade alginic acid and/ or citric acid, and sufficient sodium carbonate or bicarbonate mixtures thereof to neutralize the acidic groups of the alginic and citric acids. After swallowing, the components will react with the gastric acid to form a carbonated raft which then floats on the stomach contents.

Atyabi et al. (1996a & 1996b) developed a similar system using the ion exchange resin Dowex. The resin beads were loaded with sodiumbicarbonate and theophylline which were bound to the resin. The loaded resin beads were coated with a semipermeable membrane to overcome rapid loss of CO₂. After exposure to gastric media, exchange of bicarbonate and chloride ions took place and lead to the formation of CO₂, which was trapped within the membrane, causing the particles to float. Gastric residence time was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal. Furthermore, the system was capable of sustaining the drug release.

Chitosan based sustained release floating tablets using a mixture of NaHCO₃ and citric acid has been investigated by *Inouye et al. (1988)*. Two types of chitosan with different degrees of deacetylation, chitosan H and L, and prednisolone as a model drug

were used and two types of preparations were examined. The first were directly compressed tablets using a mixture of sodium hydrogen carbonate and citric acid, while the second was composed of a directly compressed layer coated with chitosan layer enclosing CO₂. Both formulations imparted quick buoyancy to the preparations, but the drug release from the preparation using chitosan L was slower than that of chitosan H. In a further study, the release properties were controlled by regulating the chitosan content of the granules, or the chitosan L membrane thickness of the laminated preparations (*Inouye et al., 1989*).

Double layered matrix tablets have been proposed containing an effervescent layer loaded with carbonate and optionally citric acid, using HPMC K4M and K15M (*Ingani et al., 1987*) or mixture of HPMC K 4M and polyethylene oxide (PEO) (*Fassihi, 1998; Yang et al., 1999; Yang and Fassihi, 1996*) as gelling hydrocolloid and release controlling polymer. After contact with acidic aqueous media, CO₂ is generated and entrapped within the gelling hydrocolloid, causing the system to float; meanwhile the drug was released in a sustained manner.

Floating minitables, using tartaric acid, NaHCO₃ and calcium carbonate as effervescent components and glyceryl palmitostearate as meltable binder, have been developed by *Goole et al. (2008a & 2008b)*. The system consisted of a 3 mm drug-containing gas-generating core, prepared by melt granulation and subsequent compression, and coated with a flexible polymeric membrane of Eudragit® RL 30 D. The minitables were able to float within 10 min and remained buoyant for more than 13 h, independent of the pH. In addition, the drug release was sustained for more than 12h.

Umezawa (1978) developed floating minicapsules with a diameter in the range of 0.1-2 mm and were consisting of a NaHCO₃ core, which is coated with an inner HPMC layer and an outer pepstatin layer. On contact with gastric acid, carbon dioxide is generated within the core causing the particles to float. Furthermore, the release and action of pepstatin within the stomach was prolonged, and the pepsin activity in patients with gastric and duodenal ulcers was suppressed..

Omidian et al. (2005 & 2006) developed superporous hydrogel hybrids, which are prepared by crosslinking a water-soluble or water-dispersible polymer to the formed superporous hydrogel. Examples for hybrid agents are polysaccharides, such as sodium alginate, pectin, chitosan or synthetic water-soluble hydrophilic polymers, e.g. poly(vinyl alcohol). Unlike superporous hydrogels and superporous hydrogel composites, superporous hydrogel hybrids are not easily breakable when stretched due to their highly elastic properties in the swollen state, which may be very useful for developing gastrointestinal DDS.

Jackson et al. (2000) observed extended gastric residence times of the positively charged ion-exchange resin cholestyramine, an anionic resin, due to adhering to and coating of the gastric mucosa. On the other hand, the oppositely charged cationic-exchange resin Amberlite IRP-69 did not possess the same characteristics. Such behaviors lead to concluding that the surface charge of the resin might play a significant role in mucoadhesion and subsequent retention.

Tetracycline–sucralfate complex was prepared under acidic conditions by **Higo et al. (2004)** and its mucoadhesive properties both *in vitro* and *in vivo* were evaluated. The complex showed excellent mucoadhesive properties, where higher amounts of the

complex were retained on the gastric mucosa compared with the physical mixtures of tetracycline and sucralfate.

Mucoadhesive microspheres containing drug and Carbopol® 934P have been developed, which were dispersed within a waxy matrix of polyglycerol esters of fatty acids. The microspheres were reported to prolong the GI residence of the drug after oral administration, by adhering to the stomach mucosa in rats and Mongolian gerbils, which was due to the hydration and swelling of the Carbopol in the microspheres on contact with water (*Yohko Akiyama and Nagahara, 1999*).

The unfolding system, developed by *Klausner et al. (2002)*, was composed of multilayer, polymeric films based on a drug-containing shellac matrix as the inner layer, with outer shielding layers on both sides composed of hydrolysed gelatin/ Eudragit S/ glycerine/ glutaraldehyde. The system was optionally framed with rigid polymeric strips composed of L-poly(lactic acid)/ ethylcellulose (EC). Such dosage forms were administered to beagle dogs, after placing them into gelatin capsules. The dimensions and the mechanical properties of the films influenced the *in vivo* gastric retention behaviour. Prolonged residence times and improved absorption properties could be achieved with the model drug riboflavin using a $\geq 2.5 \times 2.5$ cm large device.

In addition, levodopa-containing multilayer films were investigated in beagle dogs (*Klausner et al., 2003a*). The mean absorption time of the drug was significantly extended when it was compared to non-gastroretentive controlled release particles and oral solutions. The performance of levodopa-containing, multilayer films was also

studied in humans (*Klausner et al., 2003b*), and gastric retention for ≥ 5 h could be achieved, due to the rigidity and size of the dosage forms.

Watanabe et al. (1976) developed a single-unit, floating drug delivery system having an inherent low density, consisting of a hollow core composed of an empty hard gelatin capsule, polystyrene foam or pop rice grain, and subsequently, coated with a subcoat of cellulose acetate phthalate, and an outer drug-containing coating of EC/HPMC.

Sheth and Toussounian (1978) developed a HBS capsule containing a mixture of a drug and hydrocolloids. Upon contact with gastric fluids, the capsule shell dissolves and the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time. The same authors developed sustained release floating tablets of an active ingredient and one or more hydrocolloids such as methylcellulose, HPC, HPMC, HEC and sodium CMC, which upon contact with gastric fluid provided a water impermeable colloidal gel barrier on the surface of tablets (*Sheth, 1979a, 1979b*).

Mitra (1984) described a multilayered, flexible, sheet like medicament device that was buoyant in the gastric juice of the stomach and had sustained release characteristics. The device consisted of self supporting carrier film(s) made up of a water insoluble polymer matrix with the drug dispersed there in, and a barrier film overlaying the carrier film. The barrier film consisted of a water insoluble and a water and drug permeable polymer or copolymer. Both films were sealed together along their periphery, in such a way as to entrap a plurality of small air pockets, which imparted the laminated films their

buoyancy. The time for buoyancy and the rate of drug release can be modulated by the appropriate selection of the polymer matrix.

Ushimaru et al. (1987) developed sustained release capsules containing a mixture of a drug, a cellulose derivative or starch derivative which forms a gel in water, and a higher fatty acid glyceride or higher alcohol or a mixture thereof which is solid at room temperature (RT), with an inherent density of $< 1 \text{ g/cm}^3$.

Desai and Bolton (1993) developed controlled release floating moulded gel tablets of theophylline using agar and light mineral oil. The light mineral oil was essential for the floating property of the tablet. Additionally, it served to prevent the air entrapped within the gel matrix from escaping in the acidic environment of the stomach, due to its hydrophobicity. However, the mechanism is not yet clear. In another study, these authors developed a similar formulation without using oil.

A multiple-unit gastroretentive DDS which contained air compartments was described by *Iannuccelli et al. (1998)*. The units forming the system were composed of a calcium alginate core separated by an air compartment from a membrane of calcium alginate or calcium alginate/ polyvinyl acetate (PVA). Floating *in vitro* and *in vivo* of drug-free systems was observed. When furosemide was incorporated into the units (*Iannuccelli et al., 2000*); only 20% of the drug was released after 8 h. Therefore, a solid dispersion of furosemide/PVP was prepared to improve the drug release.



AIM AND PLAN OF WORK

3. AIM AND PLAN OF WORK

The present work is to formulate floating tablet of Amoxicillin trihydrate by direct compression method and to carry out the evaluation for the formulated tablets as per official standards. Helicobacter pylori exists in the gastric mucous layer or epithelial cell surfaces. Thus, the concentration and resident time of amoxicillin trihydrate in stomach would be effective for complete eradication of Helicobacter pylori. Amoxycillin trihydrate is considered as a good candidate for incorporation in a gastro-retentive dosage form due to its high solubility in the stomach pH compared to its solubility in the small intestine pH.

So gastro-retentive drug delivery system is desirable to prolong the residence time of the dosage form in the stomach or upper gastrointestinal tract until the drug is completely released from the system. In order to extend the gastrointestinal residence period, a gastroretentive floating drug delivery system of amoxycillin trihydrate has been developed.

To design and Develop the single unit floating matrix tablets of Amoxicillin trihydrate with different natural and synthetic polymers such as HPMC K4M, HPMC K15M, HPMC K100M by taking single polymer in the formulation.

To evaluate the physicochemical characteristics of all formulations and to carryout *in vitro* drug release studies using USP XXIV apparatus. To select the best formulation based on the above studies for stability studies.

3.1 PLAN OF WORK

1. Literature survey
2. Solubility studies of Amoxycillin trihydrate.
3. Determination of drug – excipient compatibility using FTIR studies.
4. Plotting of calibration curves of Amoxycillin trihydrate in 0.1 N HCl (pH 1.2).
5. Formulation of floating tablets of Amoxycillin trihydrate with HPMC K4M, HPMC K15M, HPMC K100M, and Xanthan gum by direct compression method by taking single polymer in the formulation.
6. Evaluation of pre-compression blend for Bulk density, Tapped density, Hausner ratio, % Compressibility index and Angle of repose. Evaluation of floating tablets of Amoxycillin trihydrate for Weight variation, Thickness, Hardness, Friability, Drug content, Floating lag time and floating duration time.
7. *In vitro* drug release studies of prepared floating tablets in 0.1 N HCl (pH 1.2) by using USP dissolution apparatus, rotating paddle type and selection of best formulation.

8. To fit the obtained data in various kinetic models & suggest a suitable mechanism of drug release.
9. Stability studies.



MATERIALS AND METHODS

4.1 MATERIALS

Table 5: 4.1.1 MATERIALS USED IN THE STUDY

Name of chemical	Source
Amoxycillin trihydrate	Hetero labs
HPMC K4M	Colorcon Asia Pvt. Limited
HPMC K15M	Colorcon Asia Pvt. Limited
HPMC K100M	Colorcon Asia Pvt. Limited
Xanthan gum	ISP ,Hyd.
Polyvinyl Pyrrolidone(K90)	ISP ,Hyd.
Microcrystalline cellulose(PH102)	Hetero lab's, Hyderabad
Sodium bicarbonate	Merck specialties Pvt. Limited
Magnesium stearate	M/S Mohan lal dayaran & Co.,
Talc	M/S Mohan lal dayaran & Co.,
Barium Sulphate	Eskay fine Chemicals, Mumbai

Table 6: 4.1.2 EQUIPMENT USED IN THE STUDY

Name of equipment	Manufacturer
Digital balance	AW 120, Shimadzu Corporation, Japan.
Tablet dissolution apparatus	Electrolab, India
Compression Machine	Riddhi, Ahmedabad, India
Roche Friabilator	Tab machines, Germany
Pfizer Hardness tester	Cadmach, Ahmedabad, India
UV/Visible Spectrophotometer	Elico, SL-159, India
Digimatic vernier callipers	Mitutoyo Corporation, China
Mechanical shaker	Remi equipments.
FT -IR Spectrophotometer	Perkin Elmer, UK

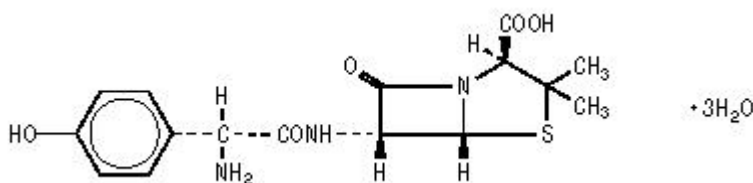
4.1.3 AMOXYCILLIN TRIHYDRATE PROFILE

Amoxycillin, formerly **amoxycillin**, **tormoxin** (in India), **amoxycillin** (cilamox) in Australia, abbreviated **amox**, is a moderate-spectrum, bacteriolytic, β -lactam antibiotic

used to treat bacterial infections caused by susceptible microorganisms. It is usually the amoxicillin trihydrate of choice within the class because it is better absorbed, following oral administration, than other β -lactam antibiotics. It is also a treatment for cystic acne.

Chemical name: (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Structure:



Molecular formula : $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_5\text{S} \cdot 3\text{H}_2\text{O}$

Molecular weight : 419.45.

Physical form : White crystalline powder

Solubility : **Highly soluble in 0.1N HCl** (shows pH dependent solubility,

decreasing with increasing pH), Slightly soluble in water, methanol and ethanol. Practically insoluble in chloroform and ether.

Melting range : 192-194 °C

PHARMACOKINETIC PARAMETERS

Bioavailability : 80-90%

Protein binding : 20%

Half-life : 1.7hrs

T_{max} : 1-2hrs

C_{max} : 5 µg/mL

Dosage : 250-575mg for every 8hrs

Log P value : 0.75

Forms: Various hydrated forms of amoxycillin, including monohydrate, dihydrate, and trihydrate have been reported among which, the trihydrate is the most stable hydrated form.

Absorption window: Upper part of GIT

Mechanism of action: Amoxycillin acts by inhibiting the synthesis of bacterial cell walls. It inhibits cross-linkage between the linear peptidoglycan polymer chains that make up a major component of the cell walls of both Gram-positive and Gram-negative bacteria.

4.1.4 POLYMER PROFILES

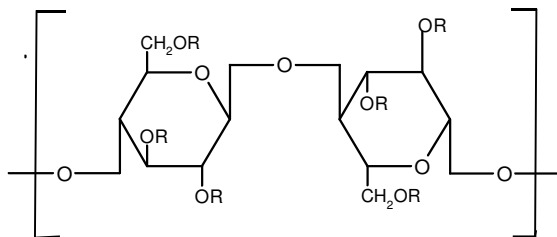
a) **4.1.4.1 HYDROXY PROPYL METHYL CELLULOSE (HPMC)****Non-proprietary names**

JP: Hydroxypropylmethylcellulose

BP: Hypromellose

Ph Eur: Methylhydroxypropylcellulosum

USP: Hypromellose

Chemical Name: Cellulose, 2-hydroxypropyl methyl ether.**Synonyms:** Methyl Hydroxy Propyl Cellulose, Propylene Glycol ether of methylcellulose, Methocel, Metolose, E464, Pharmacoat, Culminal MHPC.**Structural Formula:**Where R is H, CH₃ or CH₃-CH(OH)-CH₂**Physical and chemical properties****Molecular weight** : 10,000 – 15, 00,000**Color** : White to creamy-white**Nature** : Fibrous or granular powder**Odour** : Odourless

Taste : Tasteless

Density : 0.3-1.3 g/mL

Specific gravity : 1.26

Solubility: Soluble in cold water, practically insoluble in Chloroform, ethanol (95%) and ether but soluble in mixture of ethanol and Dichloromethane.

Viscosity: HPMC-K4M-3,000-5600mPas, K15M: 12,000-21,000 mPas

K100M: 80,000-1, 20,000 mPas.

Melting point: Browns at 190-200°C, chars at 225-230°C, Glass transition temperature is 170-180°C.

Functional category: Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Applications:

- In oral products HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. High viscosity grade may be used to retard the release of water-soluble amoxicillin trihydrate from a matrix.
- HPMC is widely used in oral and topical pharmaceutical formulations.
- Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution.

- HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products. In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments.

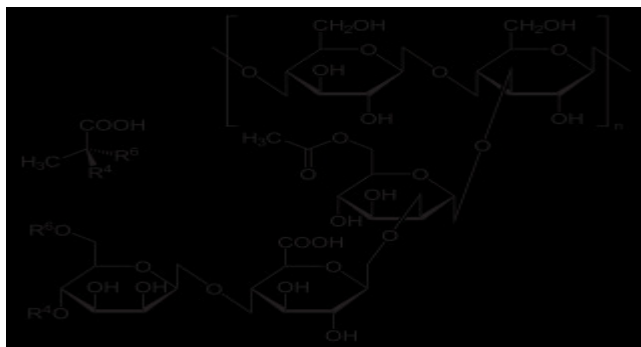
Stability and storage: It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place. Increase in temperature reduces the viscosity of the solution.

Safety: It is generally regarded as a non-toxic and non-irritant material so it is widely used in many oral and topical pharmaceutical formulations. Excessive consumption of HPMC may have laxative effect (Rowe et al., 2003).

b) 4.1.4.2 XANTHAN GUM

Xanthan Gum is a high molecular anion polysaccharide produced by fermentation of a carbohydrate with *Xanthomonas campestris*. It is completely soluble in cold or hot water.

Structure:



Molecular formula: $C_{35}H_{49}O_{29}$ (monomer)

Physical and chemical properties

Color	:	white to creamy-white,
Nature	:	occurs as a fine, hygroscopic powder
Odour	:	odorless or almost odorless
Viscosity	:	> 1575 mPas
pH	:	6.0-8.0

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution.

Functional Category: Used in Food, Dietary Supplements and Cosmetics, as a thickening or gelling agent, stabilizer, emulsifier, and texturing agent.

Pharmaceutical Applications for Xanthan Gum

- Controlled/Sustained Release Tablets
- Antibiotic suspensions/sugar-free syrups
- “Slimming Aids”
- Preparations for Dysphagics
- Barium meals (X-ray contrast media).

4.2 METHODS

4.2.1 CONSTRUCTION OF CALIBRATION CURVE:

4.2.1.1 Standard Graph of Amoxycillin Trihydrate in 0.1N HCl

The stock solution was freshly prepared by dissolving 100mg of amoxycillin trihydrate in 10ml of methanol in a 100mL volumetric flask and then making up the solution upto the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/mL (stock I). From this stock 0.1, 0.5, 1, 1.5, 2.0, 3.0 and 3.5mL were taken separately and made up to 10mL with distilled water, to produce 10, 50, 100, 150, 200, 300 and 350µg/mL respectively. The absorbance was measured at 272nm using a UV-Visible spectrophotometer (Elico, SD-159, India) against 0.1 N HCl as blank and plotted graphically to give the standard graph of amoxycillin trihydrate.

4.2.2 SOLUBILITY STUDY OF AMOXYCILLIN TRI HYDRATE:

Excess amount of amoxycillin trihydrate was placed in 0.1 N HCl in order to determine its solubility. The samples were shaken for 24 h at 37°C in a horizontal shaker. The supernatant was filtered and the filtrate was diluted with 0.1N HCl and estimated by UV/ Visible Spectrophotometer at λ_{max} of 272 nm.

4.2.3 AMOXYCILLIN TRIHYDRATE-EXCIPIENT COMPATIBILITY STUDIES:

4.2.3.1 Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure amoxicillin trihydrate, individual polymers and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1} .

4.2.4 EVALUATION OF FINAL BLEND:

The final blend of all formulations was evaluated for Bulk density, Tapped density, % Compressibility Index (CI), Hausner ratio and Angle of repose.

a) Bulk Density

30gms of material was passed through a sieve no. 25 to break up agglomerates and introduced into a 100mL dry cylinder. Without compacting, the powder was carefully levelled and the unsettled apparent volume, V_o , was read. The bulk density was calculated, in grams per mL, using the formula (Shah et al., 1997).

$$\text{Bulk density} = (M) / (V_o)$$

Where, M = Total mass of the material

b) Tapped Density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a mechanical tapped density tester

(Electrolab) that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 575 times initially followed by an additional tap of 750 times and then tapped volume V_f , was measured to the nearest graduated unit. The tapped density was calculated, in g per mL, using the formula:

$$\text{Tapped density} = (M) / (V_f)$$

c) Measures of Powder Compressibility

The % Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed.

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is a measure of the relative inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formula:

$$\% \text{ Compressibility Index} = (V_r - V_o) * 100 / V_r$$

Where, V_r = Tapped density

V_o = Bulk density

Table 7: Compressibility index specifications

Compressibility Index	Properties
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner Ratio

It indicates that the flow properties of the powder and measured by the ratio of tapped density to bulk density.

$$\text{Hausner ratio} = V_o / V_f$$

V_o = Bulk volume, V_r = Tapped volume

Table 8: Hausner Ratio Specifications

Hausner Ratio	Property
0 - 1.2	Free flowing
1.2 – 1.6	Cohesive powder

d) Angle of Repose

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height 'h' above a graph paper that was placed on a flat horizontal surface. The blend was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius, **r** of the base of the conical

pile was measured. The angle of repose, α , was calculated using the following formula: (Copper J, et al., 1986).

$$A = \tan^{-1} h/r$$

4.2.5 FORMULATION DEVELOPMENT

4.2.5.1 Preparation of Single Unit Floating Matrix Tablets of AMT

Technology Applied: Direct compression.

The key ingredients included in the formulations are:

- Hydrophilic Polymers: HPMC K4M, HPMC K15M, HPMC K100M and Xanthan gum to modify the pattern of amoxicillin trihydrate release from matrix.
- Effervescent agent: Sodium bicarbonate
- Filler: Micro Crystalline Cellulose
- Antiadherent: Talc
- Lubricant: Magnesium Stearate.

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically, to this required quantity of AMT was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no 40 and mixed with the amoxicillin trihydrate blend which was also passed through sieve no 40. The whole mixture was mixed for 3 minutes. To this Magnesium stearate was added and mixed for minutes, later Talc was added and mixed for 2 minutes. The mixture

equivalent to 850mg was compressed into tablets with 13.5mm capsulate punches at a hardness of 6 kg/cm².The composition of various formulations was given in **Table 9(a-d)**

Table 9a: Formulation trails with HPMC K4M

INGREDIENTS Weight in mg	FORMULATIONS		
	F1	F2	F3
Amoxycillin trihydrate	575	575	575
HPMC K4M	100	125	150
HPMC K15M	-	-	-
HPMC K100M	-	-	-
MCC	87	62	37
NaHCO ₃	72	72	72
Mg Stearate	8	8	8
Talc	8	8	8

Total tablet weight: 850mg

Table 9b: Formulation trails with HPMC K15M

INGREDIENTS Weight in mg	FORMULATIONS			
	F4	F5	F6	F7
Amoxycillin trihydrate	575	575	575	575
HPMC K4M	-	-	-	-
HPMC K15M	75	100	150	135
HPMC K100M	-	-	-	-
MCC	107	87	37	52
NaHCO ₃	72	72	72	72
Mg Stearate	8	8	8	8
Talc	8	8	8	8

Total tablet weight: 850mg

Table 9c: Formulation trails with HPMC K100M

INGREDIENTS Weight in mg	FORMULATIONS		
	F8	F9	F10
Amoxycillin	575	575	575
trihydrate			
HPMC K4M	-	-	-
HPMC K15M	-	-	-
HPMC K100M	50	75	100
MCC	137	112	87
NaHCO₃	72	72	72
Mg Stearate	8	8	8
Talc	8	8	8

Total tablet weight: 850mg

Table 9d: Formulation trials with combination of Xanthan gum (natural polymer) and HPMC K100M (synthetic polymer)

Ingredients (weights in mg)	Formulations		
	F11	F12	F13
Amoxycillin trihydrate	575	575	575
Xanthan gum	50	30	30
HPMC K100M	50	70	80
PVP K 90	48	48	48
MCC	71	71	61
NaHCO ₃	40	40	40
Magnesium Stearate	8	8	8
Talc	8	8	8

Total tablet weight: 850mg

4.2.5.2 Evaluation of Single Unit Floating Matrix Tablets of Amoxycillin Trihydrate

- ❖ Weight variation
- ❖ Thickness
- ❖ Hardness
- ❖ Friability
- ❖ Floating time
- ❖ Floating lag time
- ❖ Amoxycillin trihydrate content
- ❖ *In vitro* amoxycillin trihydrate release

Weight Variation test

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Table 10: Pharmacopoeial specifications for tablet weight variation

Average weight of tablets (mg) (IP)	Average weight of tablets (mg) (USP)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than 250	More than 324	5

Thickness test

The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using a Vernier Callipers. The average thickness and standard deviation were reported.

Hardness test

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 10 tablets was determined using Pfizer hardness tester and the average was calculated and presented with standard deviation.

Friability test

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = [(W_1 - W_2) / W_1] \times 100$$

Where W_1 = Initial weight of 20 tablets

W_2 = Weight of the 20 tablets after testing

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al.* The tablets were placed in a beaker containing 100 mL of 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as ***floating lag time***. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the ***total floating time***.

Determination of Drug Content

Twenty tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100 mL volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and amoxycillin trihydrate content in the samples was estimated using UV- Visible spectrophotometer at λ_{max} of 272 nm.

***In vitro* Drug Release Studies**

The *in vitro* amoxycillin trihydrate release study was performed for the single unit tablets using USP Type II dissolution apparatus under the following conditions.

Dissolution test parameters

Medium	:	900mL of 0.1N HCl
Rotation speed	:	50 rpm
Temperature	:	37±0.5°C
Sampling Volume	:	5mL
Sampling Time	:	0.5, 1, 2, 4, 6, 8, 10, 12 hours

At predetermined time intervals samples (5 mL) were collected and replenished with same volume of fresh media. The amoxycillin trihydrate content in the samples was estimated using UV- Visible spectrophotometer at λ_{max} of 272 nm.

4.2.6 KINETIC MODEL FITTING

An appropriate drug release test is required to characterize the drug product and ensure batch to batch reproducibility and consistent pharmacological/biological activity and to evaluate scale up and post approval changes such as manufacturing site changes, component and composition changes. The release of drug from a sustained release formulation is controlled by various factors through different mechanism such as diffusion, erosion or osmosis. Several mathematical models are proposed by many researchers to describe the drug release profiles from various systems. In order to characterize the kinetics of drug release from dosage forms several model dependent methods are reported by various researchers. The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data. Both the linear and non-linear models are being used in practice for dissolution modelling. Linear models include Zero order, Higuchi, Hixon - Crowell, Quadratic and Polynomials, where as the nonlinear models include First order, Weibull, KorsMeyer - Peppas, Logistic etc.

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and Reference dissolution profiles are as follows:

- Zero order kinetics
- First order kinetics
- Korsmeyer-Peppas model
- Higuchi model

A. Zero order kinetics.

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W_0 - W_t = K_0 t$$

Where, W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant.

Dividing this equation by W_0 and simplifying:

$$f_t = k_0 t$$

Where $f_t = 1 - (W_t / W_0)$ and f_t represents the fraction of drug dissolved in time t and k_0 the apparent dissolution rate constant or zero order release constant in this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled. In this way a graphical relationship between f_t versus time is established to get the Zero order constant from the slope. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of transdermal systems as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

B. First order kinetics

This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 - K_1 t / 2.303$$

Where Q_t is the amount of drug released in time t , Q_0 is initial amount of drug in the solution and K_1 is the first order release rate constant. In this way a graphical relationship is established between log percent drug remaining versus time to get the First order constant from the slope. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug remaining in its interior, in such a way, that the amount of drug released by unit of time diminishes.

C. Korsmeyer Peppas model: Korsmeyer et al., (1983) developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Q_t/Q_\infty = K_k t^n$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism. For matrix tablets, an n value of ~ 0.5 indicates diffusion – controlled mechanism while an n value of ~ 1.0 indicates erosion. Hariharan et al., 1997 suggested that if the value of n is 0.5, it indicates Fickian transport, a value of 0.5 and 1.0 non-Fickian transport, and the values close to 1.0 indicate that the system is releasing drug in a zero-order manner regardless of the actual mechanism of release (Table 11).

Table 11: Drug transport mechanism at various release exponent (n) values

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous transport (non-fickian)	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

This type of analysis of release behaviour is valuable to the formulator for comparative purposes (Hariharan et al., 1997). The release exponent can be obtained from the slope and the Constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus $\log t$.

D. Higuchi Model:

$$Q_t = K_H t^{1/2}$$

Where Q_t = the amount of drug released at time t and

K_H = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time and the concentration indicates that the drug release follows strictly Fickian diffusion.

For purpose of data treatment, the above equation is usually reduced to:

$$Q = K t^{1/2}$$

Therefore a plot of amount of drug released versus the square root of time should be linear, if drug release from the matrix is diffusion controlled. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time. An important advantage of the above equation is its simplicity.



RESULTS AND DISCUSSIONS

5.RESULTS AND DISCUSSION

5.1 CALIBRATION CURVE OF AMOXYCILLIN TRIHYDRATE IN 0.1N HCl

An UV- Visible Spectrophotometric method was used for estimation of AMT. A solution of AMT (10 µg/mL) was scanned in the wavelength range of 200-300 nm and found to have maximum absorption (λ_{\max}) at 272 nm.

Standard stock solutions of pure drug containing 100mg of AMT/100mL were prepared in 10mL of methanol and making up the volume with 0.1N HCl solution. The working standard solutions were obtained by dilution of the stock solution in 0.1N HCl. The standard curve (Figure 10) for AMT was prepared in the concentration range of 0-350µg/mL at the selected wavelength of 272nm. Their absorptivity values were used to determine the linearity (Table 13). Solutions were scanned and Beer Lamberts law limit was obeyed in concentration range of 0-350µg/mL.

Table 13: Calibration curve of AMT in 0.1N HCl at λ_{\max} 272 nm

S.NO	Concentrations(µg/mL)	Absorbance
1	0	0
2	10	0.032
3	50	0.145
4	100	0.284
5	150	0.428
6	200	0.563
7	0.828	
300		
8	350	0.964

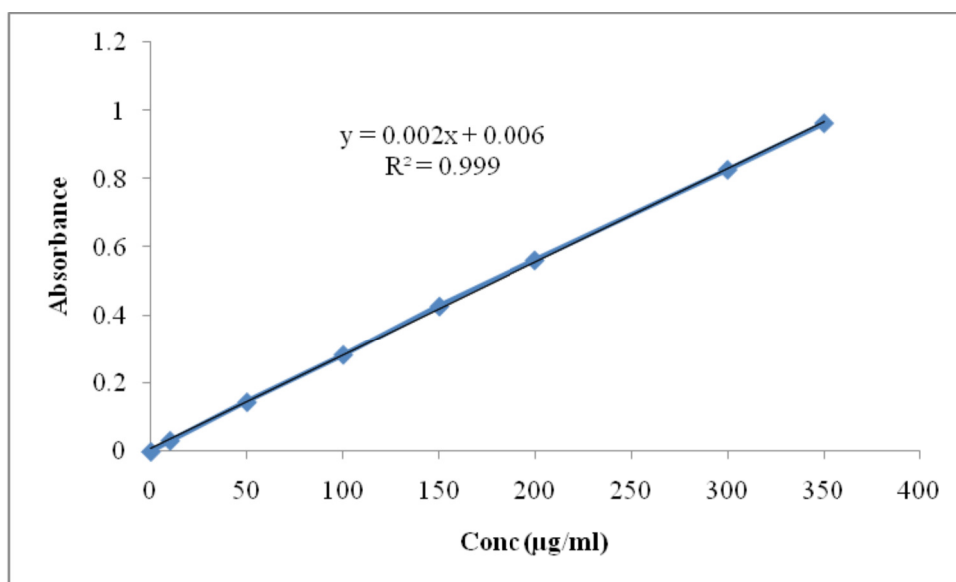


Figure 10: Standard Graph of AMT in 0.1N HCl

5.2 SOLUBILITY OF AMOXYCILLIN TRIHYDRATE

The solubility of AMT in 0.1N HCl was carried out. AMT is highly soluble in 0.1 N HCl, having quantitative solubility 139.1 mg/mL. It shows pH dependent solubility, highly soluble in acidic pH but poorly soluble in alkaline pH (as represented in Table 14).

Table 14: Solubility study data of AMT

Medium	Solubility (mg/mL)
0.1N HCl	139.1
6.8 pH phosphate buffer	4.7
Water	3.9

5.3 DRUG-EXCIPIENT COMPATIBILITY STUDIES

5.3.1 Fourier Transform Infrared (FT-IR) Spectroscopy

The thermal behavior of pure drug and the respective excipients and the binary mixture of drug and excipients are compared in the FT-IR thermograms.

The infrared (FT-IR) spectra were obtained in KBr pellet method using a perkinelmer FT-IR spectrometer spectrum from 4000 to 400 cm^{-1} .

Typical FT-IR spectra of pure Amoxycillin trihydrate (Figure 11) showed absorption at the following wave number in cm^{-1} 1775.23, 1686.51, 1578.29, 1519.61 & 1397.06.

Typical FT-IR spectra of pure xanthan gum (Figure 12) showed absorption at the following wave number in cm^{-1} 3448.04, 2924.54, 1718.20, 1654.20 & 1056.19.

Typical FT-IR spectra of pure HPMC K4M (Figure 13) showed absorption at the following wave number in cm^{-1} 3568.14, 2926.44, 1685.55, 1654.24, 1560.09, 1458.33 & 1064.45.

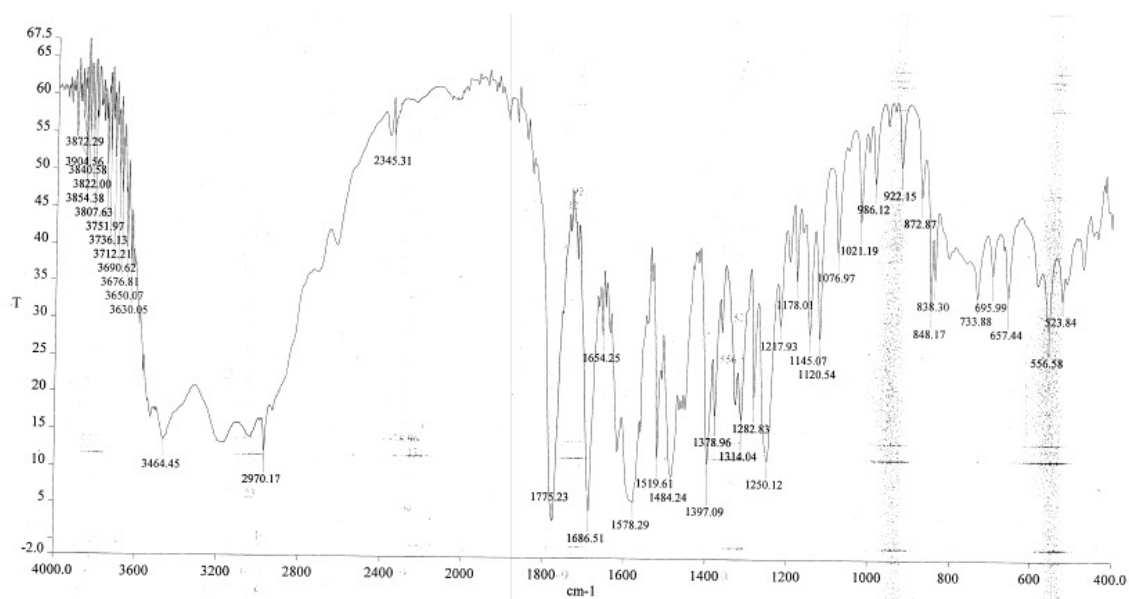


Figure 11: FTIR spectrum of Amoxicillin trihydrate

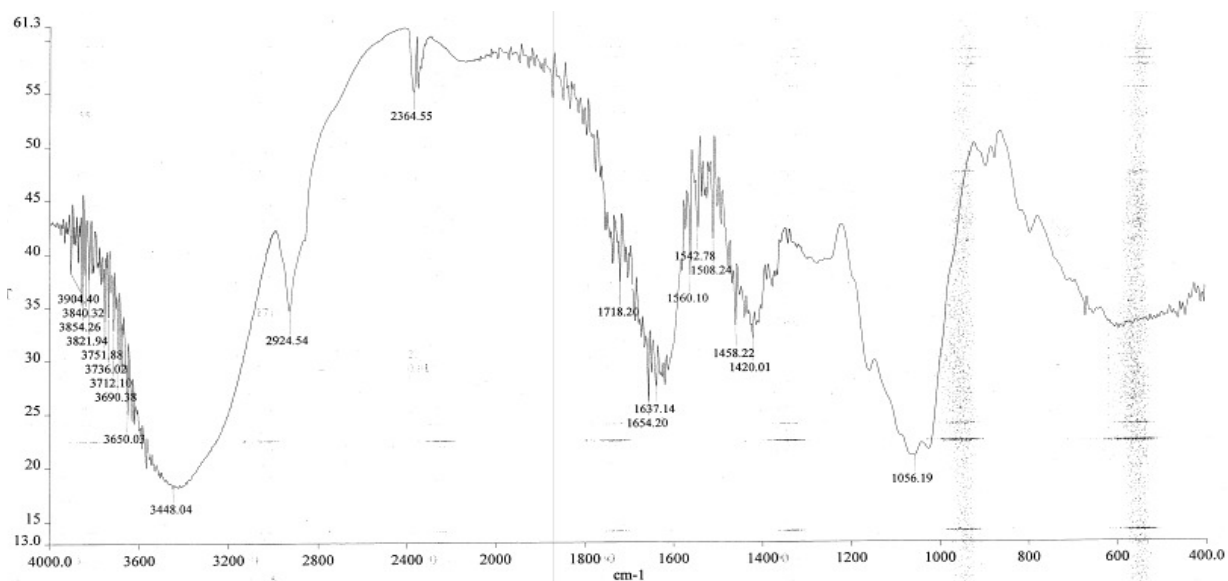


Figure 12: FTIR spectrum of xanthan gum

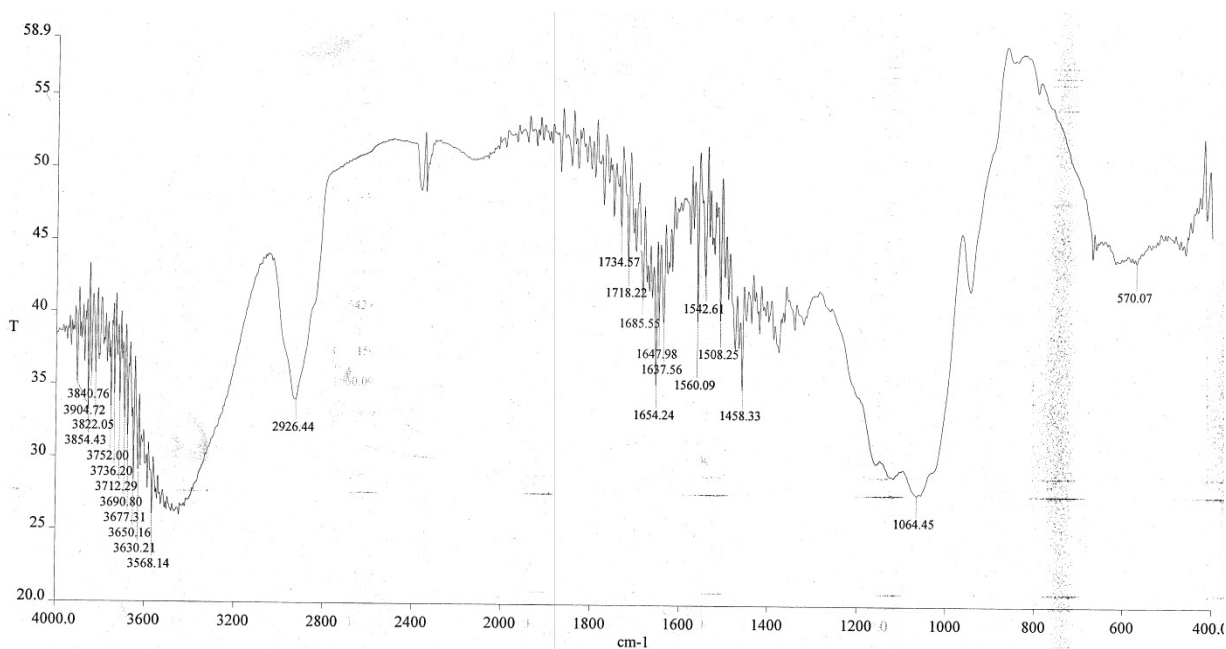


Figure 13: FTIR spectrum of Pure HPMC K4 M

The Figure 14 shows characteristics bands of Amoxycillin trihydrate which were well retained in the IR spectrum of Amoxycillin trihydrate- xanthan gum- HPMC K100M mixture without any new bands, indicating that there was no change in the structure of drug. On the basis of above report, it was concluded that Amoxycillin trihydrate is compatible with xanthan gum and HPMC K100M.

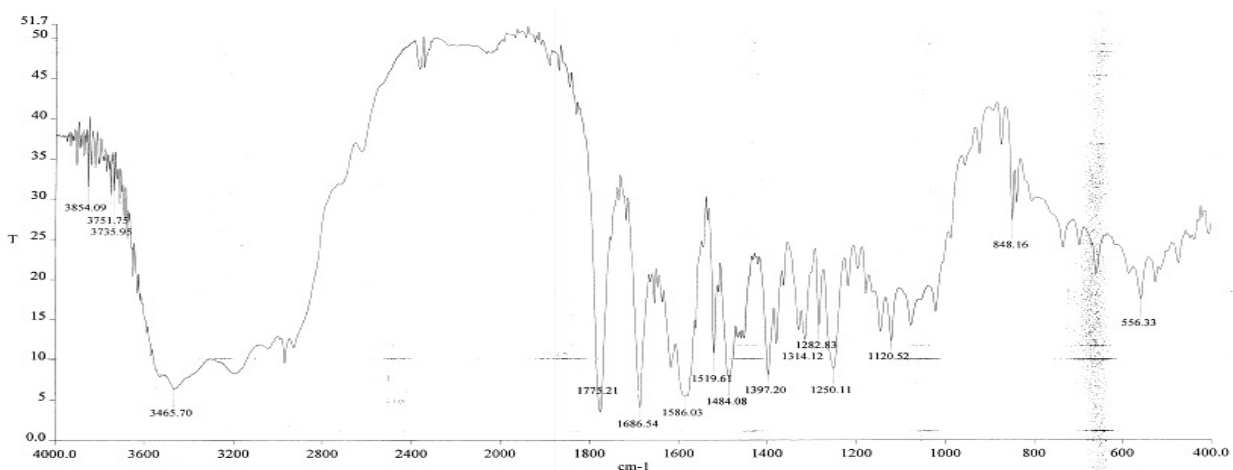


Figure 14: FTIR spectrum of Amoxycillin trihydrate with Xanthan gum and HPMC K100M

Characteristics bands of Amoxycillin trihydrate were well retained in the IR spectrum of Amoxycillin trihydrate- HPMC K4M and all other excipients in formulation without any new bands, indicating that there was no chemical incompatibility between Amoxycillin trihydrate - HPMC K15- all other excipients in formulation is showed in the Figure 15. On the basis of above results it was concluded that Amoxycillin trihydrate is compatible with HPMC K4M and all other excipients in formulation.

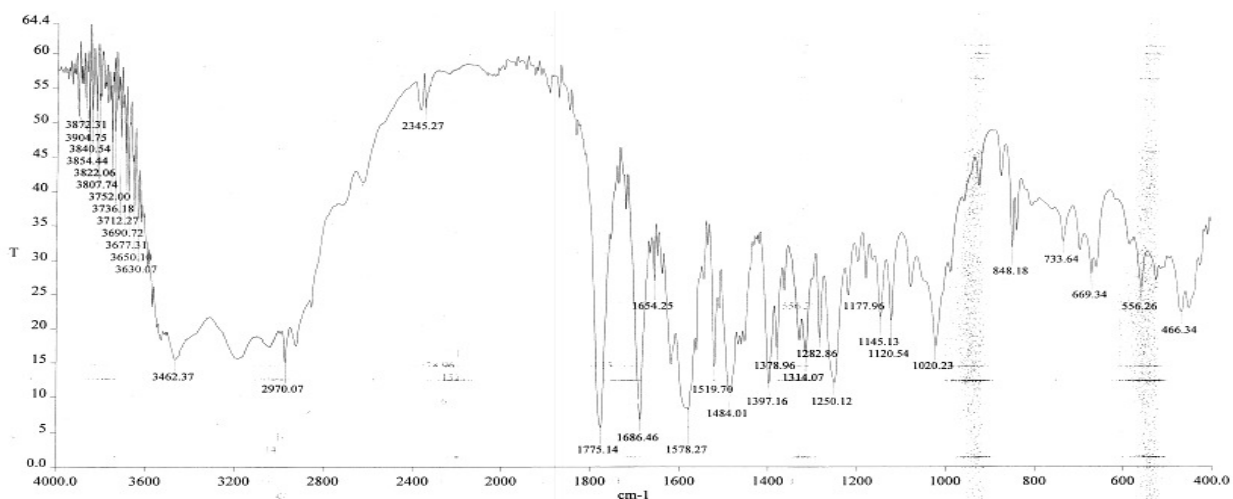


Figure 15: FTIR spectrum of Amoxycillin trihydrate with HPMC K4M and all other excipients in formulation

FTIR were used to investigate the compatibility between Amoxycillin trihydrate with excipients. The results demonstrate that there is no interaction between drug and excipients (HPMC K4M, HPMC K100M and Xanthan gum). Hence Amoxycillin trihydrate with these excipients could be used to formulate the floating tablets.

5.4 PHYSICAL PROPERTIES OF PREPARED POWDER BLENDS

Various properties of granules such as Carr's Index, Hausner's Ratio, % Compressibility index and angle of repose were determined and the results are shown in the table 15.

Table 15: Physical properties of powder blends of single unit tablet formulations

Formulations	% CI	Angle of repose	Hausner ratio
F1	15.7	29.4°	1.18
F2	12.4	28.5°	1.14
F3	11.2	29.4°	1.13
F4	15.7	29.4°	1.02
F5	12.4	28.5°	1.14
F6	11.2	29.4°	1.13
F7	13.6	28.4°	1.02
F8	12.5	26.9°	1.16
F9	14.6	27.5°	1.15
F10	12.6	27.1°	1.17
F11	15.7	29.4°	1.02
F12	12.4	28.5°	1.14
F13	11.2	29.4°	1.13

Carr's index of the granules ranged from 11.2 to 15.7 showing the granules are freely flowing (C.I = 12-16 indicating good flowing granules). Hausner's ratio of granules was found to be in the range of 1.02 to 1.18 (H.R. = 0-1.2 indicating free flowing property). The angle of repose of granules of all the formulations was found to be $\leq 30^\circ$, hence are freely flowing. The results of the physical tests of many of the blends were in the limits and comply with the standards.

5.5 EVALUATION OF PHYSICAL PARAMETERS OF SINGLE UNIT FLOATING TABLETS OF AMT

All the prepared formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeias limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 16: Physical parameters of single unit floating matrix tablets of AMT

Formulation code	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Assay (%)
F1	850.38±3.84	6.8±0.5	6.84±0.05	0.22	99.65
F2	849.52±2.87	5.9±0.2	6.76±0.06	0.37	98.65
F3	852.23±2.73	6.8±0.5	6.86±0.03	0.23	98.45
F4	848.6±2.13	6.8±0.4	6.76±0.04	0.29	99.64
F5	850.19±3.48	6.8±0.5	6.63±0.06	0.23	98.45
F6	849.71±2.3	5.9±0.2	6.65 ±0.06	0.29	99.64
F7	847.2±1.19	6.8±0.5	6.68±0.05	0.37	98.12
F8	849.46±2.27	6.5±0.3	6.55±0.25	0.23	99.72
F9	850.67±3.84	6.8±0.5	6.506±0.04	0.29	98.45
F10	848.38±3.84	6.7±0.2	6.62±0.07	0.37	99.64
F11	848.6±2.13	6.8±0.4	6.76±0.04	0.29	99.64
F12	850.19±3.48	6.8±0.5	6.63±0.06	0.23	98.45
F13	849.71±2.3	5.9±0.2	6.65 ±0.06	0.29	99.64

The results of the physical tests of the formulations were within the limits and comply with the standards. The weights of the tablets ranged from 847.2mg to 852.2mg; the weights being with $\pm 5\%$ of the average weight. The thickness was found to be in the range 6.506mm to 6.86mm. Hardness of the tablets was in the range of 5.9 to 6.8kg/cm² and friability was in the range 0.22 to 0.37%, indicating that the tablets are hard enough to withstand the external mechanical stresses. The drug content on an average was found

to be 99.72%. All these parameters were within acceptable limits. The results of the physical tests of many of the formulations were in the limits and comply with the standards.

5.6 FLOATING PROPERTIES OF SINGLE UNIT TABLETS OF AMT

All the formulations were tested for floating properties like floating lag time and total floating time. All the batches showed good *in vitro* buoyancy. The results of the *in vitro* buoyancy study were shown in Table17.

Table 17: Floating properties of single unit matrix tablets

Formulation code	Floating Lag time (sec)	Total floating time (hrs)
F1	89	>12
F2	99	>12
F3	101	>12
F4	98	>12
F5	94	>12
F6	79	>12
F7	84	>12
F8	89	>12
F9	94	>12
F10	79	>12
F11	84	>12
F12	89	>12
F13	101	>12

5.7 IN – VITRO DRUG RELEASE PROFILES

The dissolution conditions used for studying the drug release from the matrix tablets of AMT were:

Apparatus	: USP Type 2 (paddle)
Agitation speed (rpm)	: 50
Medium	: 0.1N HCl (pH 1.2), 900mL
Temperature	: $37.0 \pm 0.5^{\circ}\text{C}$
Time	: 0.5, 1, 2, 4, 6, 8, 10, and 12hr
Wavelength	: 272nm.

5.7.1 SINGLE UNIT FLOATING MATRIX TABLETS

i) Release profiles of formulations containing HPMC K4M

Table 18: Cumulative percentage drug release of formulations with HPMC K4M

Time points (hrs)	F1	F2	F3
0	0	0	0
0.5	16.84±1.89	14.40±3.56	7.25±1.76
1	31.60±3.18	25.88±3.30	16.04±3.09
2	56.27±3.01	42.75±3.08	23.01±2.66
4	83.95±1.50	58.74±0.70	38.21±1.52
6	96.71±1.30	76.63±1.16	54.23±3.05
8	----	91.07±2.02	74.43±4.59
10	----	99.71±2.39	87.79±1.28
12	----	----	98.33±2.70

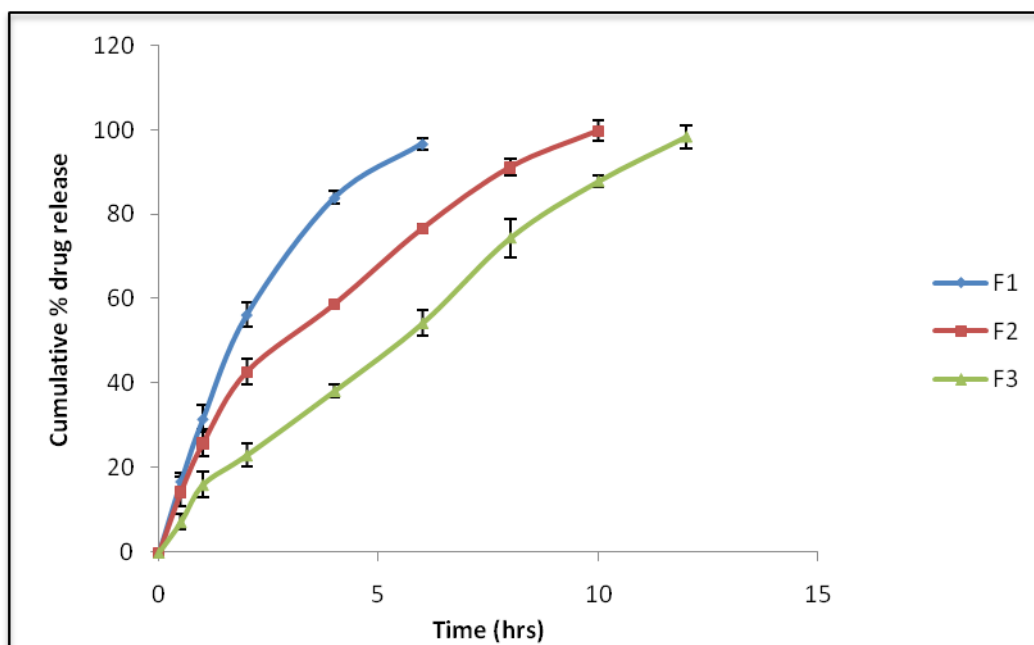


Figure 16: Cumulative % drug release of formulations containing HPMC K4M

From the above figure it can be observed that the polymer HPMC K4M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F1, F2 and F3 was 96.71% in 6hrs, 99.71% in 10hrs, and 98.3% in 12hrs respectively. Formulation F1 was unable to sustain the drug release to desired period of time (total drug was released within 6 hr). Formulations F2 was failed to release the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these three formulations floated for 12 hrs. The cumulative percent drug release from various formulations was presented in table 18. Formulation F3 was considered as best formulation among all the three formulations as it showed good buoyancy properties

(floating lag time: 101sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

ii) Release profiles of formulations containing HPMC K15M

Table 19: Cumulative percentage drug release of formulations with HPMC K15M

Time points (hrs)	F4	F5	F6	F7
0	0	0	0	0
0.5	29.34±3.21	23.59±2.05	13.54±2.11	13.68±1.91
1	42.79±2.63	32.53±3.06	14.47±1.84	15.44±0.19
2	52.63±2.57	45.40±2.03	26.58±2.94	26.25±3.30
4	83.07±2.32	68.14±1.61	36.02±3.60	37.21±4.12
6	97.24±2.28	86.40±3.15	48.14±2.22	54.08±3.69
8	----	97.60±2.01	65.25±3.08	72.76±3.83
10	----	----	76.02±3.45	85.90±3.44
12	----	----	86.49±4.47	99.80±4.51

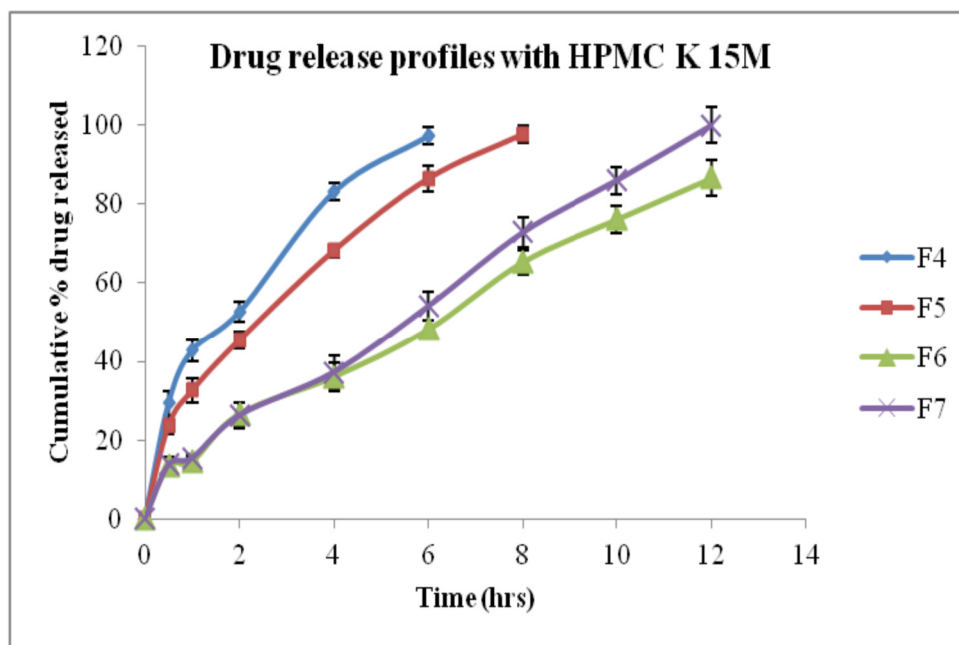


Figure 17: Cumulative % drug release of formulations containing HPMC K15M

From the above figure it is evident that the polymer HPMC K15M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F4, F5, F6, and F7 was 97.24% in 6hrs, 97.60% in 8hrs, 86.49% and 99.8% in 12hrs respectively. Formulation F4 was unable to sustain the drug release desired period of time (total drug was released within 6 hr). Formulations F5 and F6 were failed to release the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these four formulations floated for 12 hrs. The cumulative percent drug release from various formulations was represented in Table 19. Formulation F7 was considered as best formulation among all the four formulations as it showed good buoyancy properties

(floating lag time: 84 sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

iii) Release profiles of formulations containing HPMC K100M

Table 20: Cumulative percentage drug release of formulations with HPMC K100M

Time points (hrs)	F 8	F 9	F10
0	0	0	0
0.5	22.21±2.73	21.89±2.95	13.67±1.45
1	30.83±1.44	30.51±1.67	17.67±1.85
2	45.64±2.02	46.21±1.26	25.72±1.90
4	67.73±2.15	65.69±3.96	45.29±4.56
6	88.53±2.55	81.02±4.37	53.81±2.89
8	101.14±1.37	87.76±1.93	76.80±2.28
10	----	97.43±7.10	93.30±2.05
12	----	----	100.46±1.84

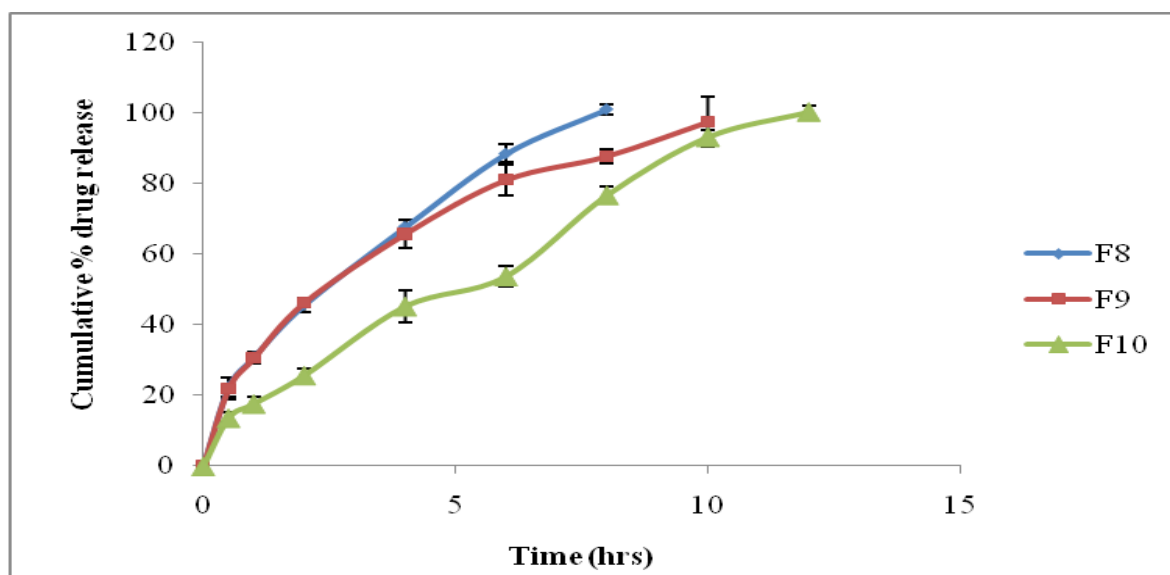


Figure 18: Cumulative % drug release of formulations containing HPMC K100M

From the above figure it is evident that the polymer HPMC K100M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F8, F9 and F10 was 101.14% in 8hrs, 97.43% in 10hrs and 100.46% in

12hrs respectively. Formulation F8 was unable to sustain the drug release desired period of time (total drug was released within 8 hr). Formulations F9 was failed to release the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these three formulations floated for 12 hrs. The cumulative percent drug release from various formulations was represented in table 20. Formulation F10 was considered as best formulation among all the three formulations as it showed good buoyancy properties (floating lag time: 79 sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

Table 21: Cumulative percentage drug release of formulations with combination of xanthan gum and HPMC K100M

Time points (hrs)	Cumulative % drug released		
	F11	F12	F13
0	0	0	0
0.5	28.04±2.59	17.87±2.032	6.045±1.48
1	36.17±2.24	25.58±2.70	17.82±1.04
2	48.16±3.49	46.60±2.80	24.02±1.37
3	60.73±1.91	57.91±2.57	39.73±0.92
4	75.45±2.79	62.52±1.41	52.24±1.66
6	87.50±1.92	76.93±1.00	67.10±1.74
8	101.45±1.99	90.80±1.54	79.50±0.92
10	----	103.56±1.98	87.14±1.96
12	----	----	100.08±3.73

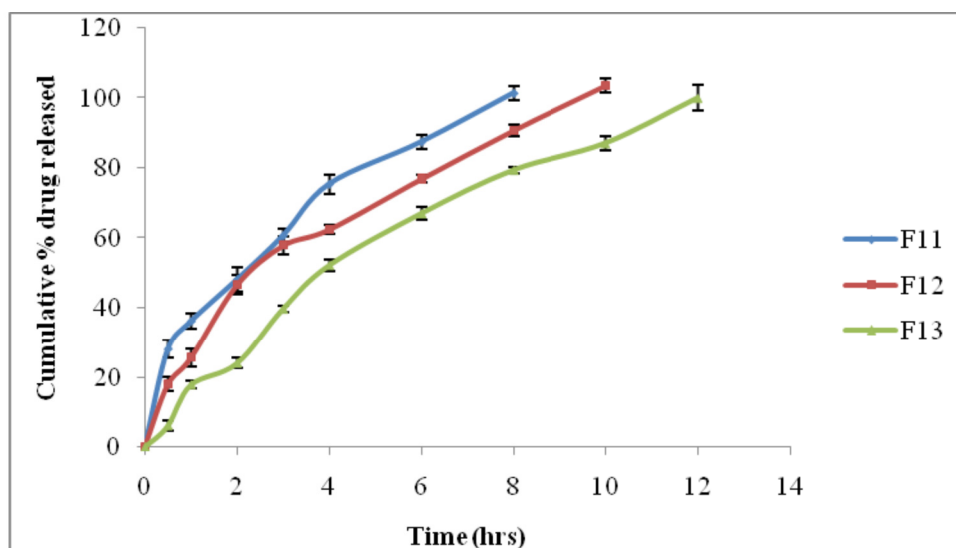


Figure 19: Cumulative percentage drug release of formulations with combination of xanthan gum and HPMC K100M

From the above figure it can be observed that the polymers having xanthan gum and HPMC K100M sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F11, F12 and F13 was 101.45% in 8hrs, 103.56% in 10hrs and 100.08% in 12hrs respectively. Formulation F11 was unable to sustain the drug release desired period of time (total drug was released within 8 hr). Formulations F12 failed to release the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymers. All these three formulations floated for 12 hrs. The cumulative percent drug release from various formulations was represented in table 21. Formulation F13 was considered as best formulation among all the three formulations as

it showed good buoyancy properties (floating lag time: 101sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

5.8 MATHEMATICAL MODELING OF DISSOLUTION PROFILES

Table 22: Regression coefficient (R^2) values of single unit floating matrix tablets for different kinetic models

Formulation	R^2 value				n value
	Zero-order	First order	Higuchi	Korsmeyer- Peppas	
F1	0.9300	0.9800	0.9803	0.9776	0.620
F2	0.9400	0.8100	0.9939	0.9937	0.580
F3	0.9920	0.8750	0.9590	0.9890	0.763
F4	0.9060	0.9588	0.9947	0.9760	0.480
F5	0.9370	0.9370	0.9981	0.9980	0.540
F6	0.9840	0.9730	0.9690	0.9890	0.700
F7	0.9918	0.9470	0.9570	0.9911	0.746
F8	0.9500	0.9740	0.9950	0.9990	0.578
F9	0.9080	0.9490	0.9960	0.9930	0.502
F10	0.9850	0.8853	0.9630	0.9890	0.721
F11	0.9114	0.9876	0.9963	0.9926	0.508
F12	0.9251	0.9782	0.9936	0.9775	0.572
F13	0.9599	0.9946	0.9766	0.9815	0.726

Drug release kinetics of formulations F1, F2 and F3 containing a HPMC K4M at a Drug:Polymer ratio of 1:0.17, 1:0.22 and 1:0.26 are shown in the table 22. From the correlation coefficient values it was evidenced that formulations F1 and F2 released drug by Higuchi model. The optimized formulation F3 released drug by Zero-order release complying with higher correlation coefficient values of **0.9920** for Zero-order equation. The drug release mechanism for all the three formulations was governed by non-fickian diffusion which was confirmed by their release exponent (n) values.

Drug release kinetics of formulations F4, F5, F6 and F7 containing a HPMC K15M at a Drug:Polymer ratio of 1:0.13, 1:0.17, 1:0.26 and 1:0.23 are shown in the table 22. From the correlation coefficient values it was evidenced that formulations F4 and F5 released drug by Higuchi model. Formulation F6 released drug by Korsmeyer-Peppas model. The optimized formulation F7 released drug by Zero-order release complying with higher correlation coefficient values of **0.9918** for Zero-order equation. The drug release mechanism for all the four formulations was governed by non-fickian diffusion which was confirmed by their release exponent (n) values.

Drug release kinetics of formulations F8, F9 and F10 containing a HPMC K100M at a Drug:Polymer ratio of 1:0.09, 1:0.13 and 1:0.17 are shown in the table 22. From the correlation coefficient values it was evidenced that formulations F8 and F10 released drug by Korsmeyer-Peppas model. The formulation F9 released drug by Higuchi model. The drug release mechanism for all the three formulations was governed by non-fickian diffusion which was confirmed by their release exponent (n) values.

Drug release kinetics of formulations F11, F12 and F13 containing a Xanthan gum and HPMC K100M at a Drug: xanthan gum: HPMC K100M ratio of 1:0.09:0.09, 1:0.06:0.12 and 1:0.04:0.14 are shown in the table 22. From the correlation coefficient values it was evidenced that formulations F11 and F12 released drug by Higuchi model. The optimized formulation F13 released drug by First-order release complying with higher correlation coefficient values of **0.9946** for First-order equation. The drug release mechanism for all the three formulations was governed by non-fickian diffusion which was confirmed by their release exponent (n) values.

The formulation F13 showed high regression value of 0.9946 for Higuchi order with complete drug release in 12 hrs made it to be selected as an optimized formulation compared with other formulations.

5.9 STABILITY STUDIES:

5.9.1 Introduction:

Storage conditions recommended

General case

Table No. 23 Testing frequency for different storage conditions

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C + 2°C/60% RH + 5% RH or 30°C + 2°C/65% RH + 5% RH	12 months
Intermediate**	30°C + 2°C/65% RH + 5% RH	6 months
Accelerated	40°C + 2°C/75% RH + 5% RH	6 months

* It is up to the applicant to decide whether long term stability studies are performed at 25 + 2°C/60% RH + 5% RH or 30 °C + 2°C/65% RH + 5% RH.

**If 30°C + 2°C/65% RH + 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C+ 2°C/60% RH + 5% RH and “significant change” occurs at any time during 6 months’ testing at the accelerated storage condition,

additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

Stability Testing for Established Drug Substances

WHO has issued guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage form. The stability of finished pharmaceutical products depends on environmental factors and on product related factors. So stability considerations should be given, the highest priority in the design and formulation of a product. The shelf life should be established with due regard to the climatic zones. To ensure both patient safety and the rational management of drug supplies, it is important that the expiry date and storage conditions are properly indicated on the label.

Accelerated stability testing

These are the studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programme. The data thus obtained, in addition to those derived from real – time stability studies, may be used to assess longer – term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes. These are also known as stress testing studies.

Expiry date

The date given on the individual container of a drug product up to and including which the product is expected to remain within specifications if stored correctly. It is established for each batch by adding the shelf-life period to the date of manufacture.

Mean Kinetic Temperature

The single test temperature for a drug product corresponding to the effects on chemical reaction kinetics of a given temperature – time distribution. A mean kinetic temperature is calculated for each of the four world climatic zones according to the formula developed by a scientist known as Hayanes. It is normally higher than the arithmetic mean temperature.

Real time (Long term) stability studies

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the shelf life, to confirm the projected shelf life and to recommend storage conditions.

Stability tests

A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilization period under specified packaging and storage conditions.

The following table gives the main objectives and uses the different types of stability testing

Table No. 24 Objectives of Stability Testing

Objective	Type of study	Use
To select adequate (from the viewpoint of stability) formulations and container-closure systems	Accelerated	Development of the product
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-life	Real-time	Registration dossier
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real-time	Quality assurance in general, including quality control.

Test Samples

For established products the following schedule is suggested by WHO:

- One batch every other year for formulations considered to be stable, otherwise one batch per year.
- One batch every 3 – 5 years for formulations for which the stability profile has been established, unless a major change has been made, e.g. in the formulation or the method of manufacture.

5.9.2 Experimental work

The Amoxycillin trihydrate Tablets of F13 was packed in HDPE bottles with Child Resistance Caps (CRC) and induction sealed. These bottles were charged for stability study at 40°C / 75% RH.

Sampling time points: Initial, 1month, 2months

Evaluation parameters: Appearance and physical parameters of tablets, Assay and % drug dissolved.

After one month

Table No. 25 Physical evaluation for stability studies of optimized formulations

	Initial	40°C / 75% RH
Colour	white	white
Thickness (mm)	6.65mm	6.64 mm
Hardness (kp)	5.9-6.0	5.8-5.9
Weight (mg)	849.71±2.3	849.61±1.9
Assay	99.64%	99.40%

Table No. 26 Percentage Cumulative release of stability studies of optimized formulation (F13) at 40°C / 75% RH for 1 month

Time (hours)	Cumulative % drug release for 1 month	
	Intial	40°C / 75% RH
0	0	0
0.5	6.045	6.045
1	17.82	17.79
2	24.02	24
3	39.73	39.69
4	52.24	52.19
6	67.10	66.90
8	79.50	78.94
10	87.14	86.99
12	100.08	99.97

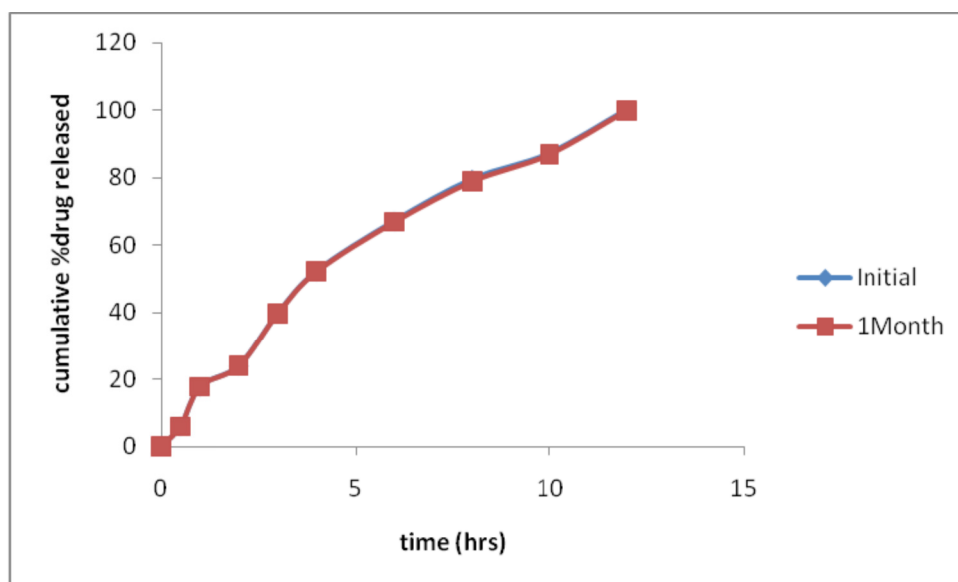


Fig No.20 Dissolution profiles of 1 months stability samples at 40°C / 75% RH

After two month

Table No. 27 Physical evaluation for stability studies of optimized formulations

	Initial	40°C / 75% RH
Colour	White	White
Surface	Smooth	Smooth
Thickness (mm)	6.65 mm	6.60 mm
Hardness (kp)	5.9-6.0	5.6-5.8
Wight (mg)	849.71±2.3	849±1.0
Assay	99.64%	99.04%

Table No. 28 Percentage Cumulative release of stability studies of optimized formulation (F13) at 40°C / 75% RH for two month

Time (hours)	Cumulative % drug release for 2 month	
	Intial	40 ⁰ C / 75% RH
0	0	0
0.5	6.045	6.045
1	17.82	17.60
2	24.02	23.81
3	39.73	39.03
4	52.24	52
6	67.10	66
8	79.50	78.10
10	87.14	86.09
12	100.08	99.04

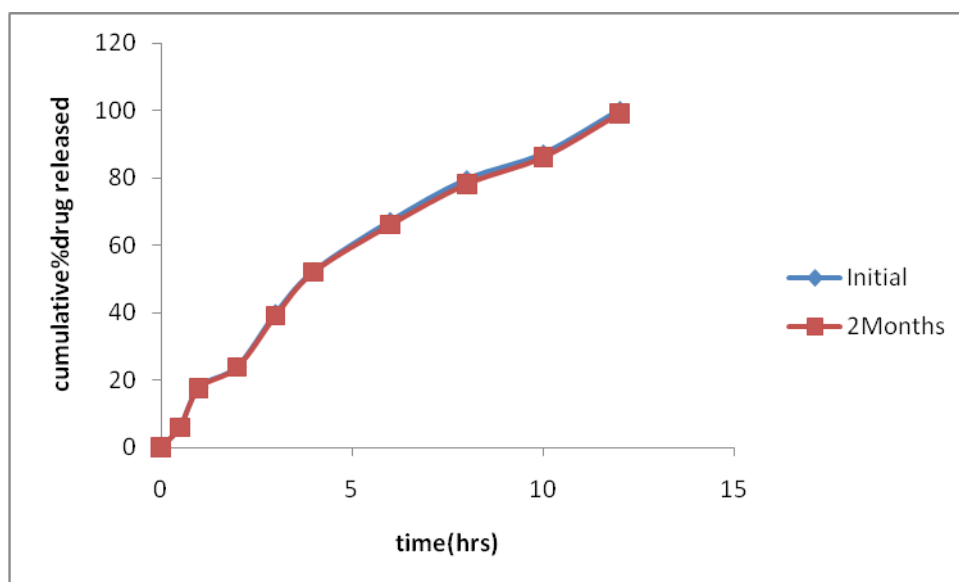


Fig No.21 Dissolution profiles of 2 months stability samples at 40°C / 75% RH

Optimized formulation (F13) was kept for stability studies, and observed that assay after 1st, 2nd month was complies with optimized formulation. Dissolution profile of stability samples after 1st, 2nd months were compared with formulation (F13). There is no significant change in *In vitro* release profile in both conditions when compared with F13. It shows that it is stable formulation.



SUMMARY AND CONCLUSION

6. SUMMARY AND CONCLUSION

SUMMARY

In the present work attempts have been made to formulate floating tablets of Amoxicillin trihydrate with HPMC K4M, HPMC K15M, HPMC K100M, and Xanthan gum by direct compression method by taking single polymer in the formulation. Amoxicillin trihydrate has shown high solubility in 0.1N HCl. Therefore it was considered as a good candidate for gastro retentive dosage form

The development of gastro retentive floating drug delivery system of Amoxicillin trihydrate, to increase gastric residence time and thereby its therapeutic efficacy against *H. Pylori* in single unit floating matrix tablets with different natural and synthetic polymers meets all the ideal characteristics to formulate in the form of floating tablets.

Based on the studies of the APIs organoleptic properties were complied with the BP and IP specifications. Physical properties such as bulk density and tapped density, angle of repose, carr's index, hausners ratio were within official standards.

Systematic studies were conducted for the preparation of floating delivery systems of Amoxycillin trihydrate. FT-IR studies showed no incompatibility between drug, polymer and various excipients used in the formulations.

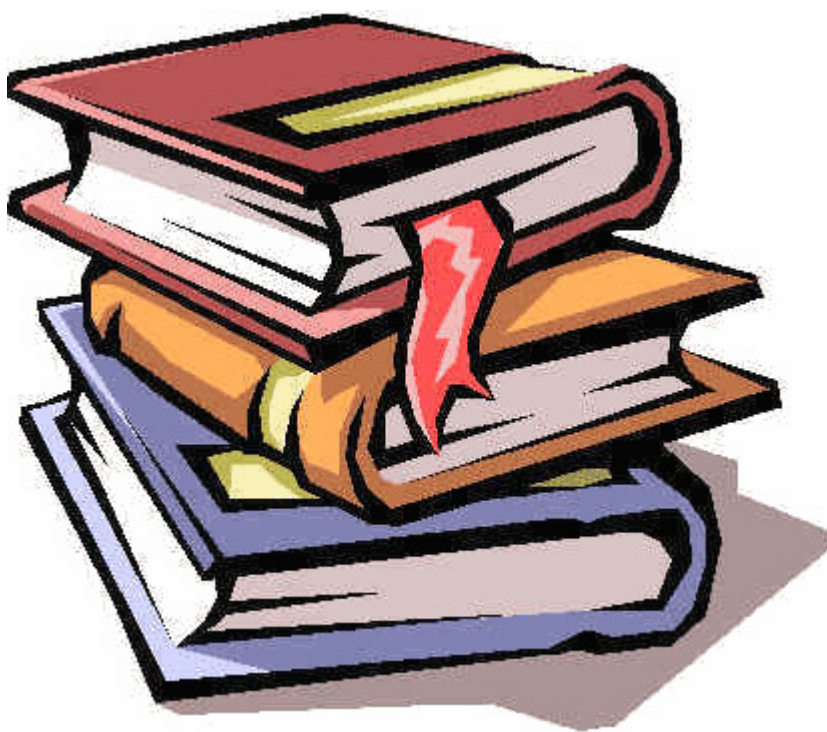
Formulated tablets gave satisfactory results for various evaluation parameters like tablet dimensions, hardness, weight variation, friability, content uniformity, *in vitro* buoyancy properties and *in vitro* drug release.

CONCLUSION

The present study shows that Amoxicillin trihydrate can be made into floating tablet dosage form by direct compression technique.

Amoxicillin trihydrate floating tablets with HPMC K4M, HPMC K15M, HPMC K100M, and Xanthan gum by taking single polymer in the formulations in which F3, F7, F10 and F13 gave better controlled drug release and floating properties in comparison to the other formulations. From the correlation coefficient values, the drug release from the optimized formulations F3 and F7 followed Zero-order pattern, F10 and F13 followed Higuchi and First-order pattern respectively. The transport of drug from all the formulations was governed by Non-Fickian mechanism which was confirmed by release exponent 'n' values of Koresmeyer Peppas equations.

Dissolution profile of stability samples after 1st, 2nd months were compared with formulation (F13). There is no significant change in *In vitro* release profile in both conditions when compared with F13. It shows that it is stable formulation



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